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VOLUME 7 NUMBER 2

# AMERICAN JOURNAL

OF

# DISEASES OF CHILDREN

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FEBUARY, 1914

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO, ILL.

ENTERED AS SECOND-CLASS MATTER, JANUARY 4, 1911, AT THE POST-OFFICE AT CHICAGO, ILLINOIS, UNDER ACT OF CONGRESS OF MARCH 3, 1879

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American Journal of Diseases of Children

VOL. 7 FEBUARY, 1914 No. 2

# BACTERIOLOGICAL DIAGNOSIS AND TREATMENT OF ALIMENTARY DISEASE IN THE INFANT AND CHILD

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The study of the bacteriology of the alimentary canal in the infant and child is so essentially a study of the behavior of bacteria in varying conditions that a consideration of the normal and abnormal bacteriology of milk is of the first importance. Since milk is the natural diet of infancy, we are compelled, in endeavoring to appraise the actual nature and extent of the pathological condition found in any given case, to consider the precise circumstances in which the same or allied processes occur in milk outside the body; for, by experimentally reproducing in the laboratory test-tube the biochemical processes taking place in the alimentary canal, we are seeking to establish these fundamental correlations which are essential to accurate and scientific diagnosis. It is further of importance that we should be able to appreciate the nature of the biochemical processes occurring under normal conditions, for we can scarcely be in a position to understand the abnormal unless we are acquainted with the normal processes, while we can only estimate the extent and nature of disorder by the measure of its departure from the conditions of health.

In the following classification I have grouped the organisms according to the conditions determining their growth in and their action on milk.

1. *Bacteria producing lactic acid, but not producing gas.* This group is represented by the *Streptococcus lacticus* and the *Bacillus lacticus.*

The *Streptococcus lacticus* (Fig. 1) is the typical organism growing in pure milk at 38 C. At a later stage when the acidity has become too

* Submitted for publication Nov. 16, 1913.

* Presented before the Pediatric Society, New York Academy of Medicine, Nov. 13, 1913.

great for the streptococcus, the *Bacillus lacticus* (Figs. 2 and 3) appears, for this organism is exceptionally tolerant of acid.

2. *Bacteria producing lactic acid, carbon dioxid and alcohol.* This group embraces the whole of the colon organisms and includes the *Bacillus acidi lactici* (Hueppe) *Bacterium acidi lactici* (Esten) *Bacillus lactis aërogenes* (Escherich) and the *Bacillus coli communis* (Figs. 4 to 7). When pure raw milk is incubated the growth of the organisms belonging to this group is inhibited by the growth of the organisms belonging to the first group. When milk, however, is grossly contaminated by colon organisms these may acquire dominance, and in such cases the curdled milk shows evidence of gas production.

3. *Bacteria growing in "pasteurized" milk,* that is, milk that has been subjected to a temperature between 65 C. and 100 C. The *Bacillus putrificus* (Fig. 8) and the *Bacillus aërogenes capsulatus* (Fig. 9) are examples of this group and their products are of a highly irritant and dangerous character.

4. *Bacteria growing in milk after it has been raised to 100 C.,* owing to the fact that their spores have not been destroyed. These organisms are found in milk that has been boiled or "sterilized" and in condensed milk. The group embraces a large number of organisms, the chief representatives being the *Bacillus subtilis,* the *Bacillus mesentericus* and the *Bacillus mesentericus vulgatus* (Figs. 10 to 15). When they develop in the intestine extremely powerful poisons of an alkaloidal character are created and the adsorption of these poisons produces profound coma and death.[1]

These organisms are quite unable to grow in raw milk, for their growth is entirely prevented by the acid-forming bacteria. The *Bacillus proteus vulgaris* is a powerful putrefactive organism, but it does not belong to this group, as it does not possess spores.

Recently "Pasteurization" has been advocated at an exceptionally low temperature — 140 F. (60 C.) for twenty minutes, and this year I have carried out a series of examinations to determine the effects of "pasteurization" at this temperature. I briefly summarize the results.

### RESULTS ON BACTERIAL FLORA OF PASTEURIZATION AT LOW TEMPERATURES

The lactic organisms were not destroyed, as they finally appeared after long incubation in all cases. But they were so greatly injured that in the great majority of the experiments they failed to appear at all in twenty-four hours, while the effect of their being unable to develop is shown by the organisms which actually developed during this period (Fig. 16).

1. Vincent: Acute Intestinal Toxemia in Infants, London, 1911.

These included the *Bacillus megatherium*, the ***Bacillus subtilis***, the *Bacillus mesentericus* and the *Bacillus aërogenes capsulatus*. The uncertain effect of "Pasteurization" at this temperature is shown by this list, for it is generally possible to specify the organism that will appear, given the temperature and time of exposure. The uncertainty is, however, in this instance not surprising, as the employment of such a low temperature is in reality an endeavor to obtain the impossible — that is, a method of pasteurization which shall certainly destroy pathogenic organisms without destroying the lactic organisms.

The grave alteration of the milk is shown in the development of acidity and the time of curdling. Fresh milk always curdles at 38 C., within twenty-four hours. It generally curdles in about eighteen hours, the acidity being about 60 to 70 degrees. In the pasteurized milk the average time of curdling was fifty-five hours, while the average acidity at the end of twenty-four hours incubation was 20 degrees, which is only very slightly above the acidity of milk at the time of milking. (Pasteurized milk immediately after pasteurization almost invariably shows a slightly higher acidity than the raw milk immediately before it is heated.)

These facts demonstrate the extreme importance of the actual conditions of the medium in determining the growth and development of the organisms. In a raw milk the *Bacillus aërogenes capsulatus* never develops. If a milk be heated at 170 F. it is nearly certain that one organism will appear on incubation in nearly pure culture — the *Bacillus putrificus*—despite the fact that there are numerous other organisms in the milk ready to develop if only the conditions are favorable; if the *Bacillus putrificus* is capable of developing then it will prevent the development of the other organisms. Similarly, if the temperature is too high for the *Bacillus putrificus* to escape destruction then the *Bacillus aërogenes capsulatus* will probably develop and hold back all the organisms of the subtilis type.

In pure milk the *Streptococcus lacticus* is the predominant organism. The more pure the milk the more free the growth of the streptococcus. At 38 C. it grows characteristically in chains. The luxuriant chain formation (Fig. 17) so frequently seen after about eight hours' incubation at blood temperature is typical of the growth of the organism in pure raw milk. Growing in sterilized milk in pure culture the streptococcus never shows this luxuriant growth (Fig. 18). The *Streptococcus lacticus* produces a moderate amount of acid, so that pure raw milk incubated at 38 C. curdles in from eighteen to twenty-four hours; incubated at 19 C. the milk should not curdle under about seventy-two hours, the curd being smooth and homogeneous.

If the milk is contaminated the growth of the streptococcus is interfered with, and colon organisms develop at an early stage with the result

that the curd is pitted, while if the gas production is excessive the curd may be brought to the surface of the milk.

After about seventy-two hours at 19 C. various forms of the "fungi" known as "moulds" (Figs. 19 and 20) begin to develop, their growth being promoted by a considerable amount of acid. At 38 C. these organisms do not appear, as the temperature is too high for them. The organisms growing in pure milk at 38 C. are confined practically to three. The *Streptococcus lacticus* grows rapidly for about twenty-four hours; at the end of this period it ceases to grow, owing to the inhibitory effect of the acid it has produced. For about forty-eight hours, as a rule, no further development is seen. Two other organisms then make their appearance — the *Bacillus lacticus* and *Saccharomycetes* (yeasts) (Fig. 21). When we consider the variety of organisms that may be isolated from the purest milk and at the same time observe the few organisms that actually grow in raw milk at its natural temperature, we realize how fallacious any conclusions drawn from bacterial growth may be, unless we fully take into account the selective properties of the particular medium in which the organisms have developed.

Milk is always acid at the time of milking. The *initial acidity* varies between 15 and 18 degrees. The *development* of acidity is due entirely to the action of micro-organisms and consequently the temperature at which milk is kept and the time of exposure to this temperature are the chief factors determining the rate at which acid is produced. The production of acid, however, does not proceed regularly. A remarkable feature connected with the development of the streptococcus is that there are two stages in its growth: (1) a stage lasting for from eight to twelve hours in which the production of acid is very slight; (2) a second stage of about twelve hours in which there is rapid production of acid. This is clearly shown in the following table, which gives the acidity in milk inoculated at 38 C., the estimation of acid being made at intervals of four hours.[2]

Degrees of acidity above the initial acidity:

| | | |
|---|---|---|
| First | four hours | 1 degree |
| Second | four hours | 2 degrees |
| Third | four hours | 4 degrees |
| Fourth | four hours | 17 degrees |
| Fifth | four hours | 36 degrees |
| Sixth | four hours | 48 degrees |

## FACTORS IN PUTREFACTION

The contents of the small intestine are normally acid, owing to the formation of lactic acid from lactose by the lactic bacteria. The normal

2. For a fuller account of the phenomena of acid development in milk see Vincent, "On the Development of Acidity in Cow's Milk and Its Relation to Time and Temperature," Glasgow Medical Journal, December, 1911; and "Nutrition of the Infant," Ed. 4, London, 1913.

dejection contains no lactose, and as a result partly of the absorption of sugar and partly of its fermentation, the lactose-content is continually diminishing as the food products pass through the alimentary canal, till, in the lower part of the colon, there is none at all. It is important to bear in mind this gradual elimination of lactose, for it constitutes the chief explanation of the difference between the *flora* of the small and of the large intestine.

Were it not for the acid condition, putrefactive processes would occur. All the conditions favoring the action of the proteolytic bacteria are present save one. Absence of acidity is the essential condition of putrefaction and consequently the presence of acid prevents its occurrence. In the large intestine the acidity steadily diminishes so that the intestinal dejecta when they reach the soil do not contain any marked excess of acid. Not infrequently the normal dejection is amphoteric.

In the soil the conditions are reversed, for putrefaction is the essential process by means of which dead organic matter is decomposed and rendered available for the vegetable kingdom, so that an acid soil is pathological.

The statement in regard to the effect of acidity is absolute as regards the obligate proteolytic organisms—that is, the subtilis group—but it is relative as regards the colon organisms. The coliform bacilli can act in an alkaline medium and also in an acid medium, but in the latter case the acid must be moderate in amount. In certain circumstances they will grow in raw milk, but at blood temperature only in about the first twelve hours of incubation. After that the acid produced will be too much for them. When the milk is pure they do not grow at all. Thus the colon organisms are intermediate, both in regard to their facultative properties and in regard to the media in which they can develop, between the lactic organisms on the one hand and the absolutely putrefactive organisms on the other hand.

The colon organisms are active in sewage, especially in its concentrated form, while when the sewage is distributed and becomes merged with the soil these organisms are replaced by the organisms of the obligate proteolytic type.

With regard to the term "putrefaction," it is perhaps well to point out that the term is used in the present connection as a synonym for proteolysis. The production of evil-smelling products is an incident of putrefaction; some organisms give rise to products with most unpleasant odor, others, notably the *Bacillus mesentericus vulgatus*, grow in profusion without creating any change that can be detected by sight, taste or smell. Indeed it is one of the grave dangers of "pasteurized" milk that the milk may be loaded with organisms of this character without there being any obvious change to suggest that the milk is not wholesome.

I may cite one experiment which illustrates the effects of the bacteriological condition of the soil on vegetation. A bulk sample of soil was divided between two pots; one pot was then pasteurized while in the other pot the soil was allowed to remain in its natural condition. Beans were then planted. The more luxuriant growth occurred in the pasteurized soil, for the acid organisms present in the untreated soil hindered the action of the putrefactive organisms. It is well known that lime is essential to the soil. In its absence the acidity created by the acid-forming organisms fails to be neutralized, with the result that the land becomes "sour" and will produce nothing but rank vegetation.

At present our studies of intestinal bacteriology are much hampered by the use of the words "infective" and "pathogenic." We need to realize that in regard to intestinal conditions such terminology is very misleading, for it tends to conceal the nature of the problem with which we have to deal. Agricultural bacteriology affords us a much better conception of the nature of the problems appertaining to intestinal conditions than does the bacteriology dealing with "specific pathogenic" organisms. A study of the bacteriology of the soil and the conditions favoring or hindering the growth of crops places us in a position to grasp the essential nature of the biochemical processes occurring in the alimentary canal: for in this study of comparative bacteriology we are confronted with the ultimate problems underlying the synthesis of the animal and vegetable kingdom.

### BACTERIOLOGY OF INTESTINAL DEJECTA

The bacteriological examination of the intestinal *dejecta* may now be discussed. Since everything depends on accurate recognition of the organisms, the microscopical equipment must be of the highest quality. After considerable experience I strongly recommend the complete Zeiss microscope as the most workman-like and efficient instrument. The condenser should be the Aplanatic of N. A. 1.4 and the chief objective employed should be the 2 mm. Apochromatic of N. A. 1.4. A nose piece should not be employed as the objective is never accurately centered to the optical axis when this is used. The eyepiece generally most convenient is the compensating ocular No. 6. These details are worth mentioning since, as a rule, medical men do not appear to have paid sufficient attention to the fact that bacteriological work calls for the greatest accuracy in the optical apparatus.

The methods of bacteriological diagnosis adopted have been gradually worked out in my laboratory as the result of some years practical study of the problems involved, and before entering on the details I wish to acknowledge my great indebtedness to my friend and colleague, Mr. Robert Mond, Treasurer of The Infants Hospital. The whole of

my investigations have been carried out in the hospital and laboratory built and equipped by him.

The methods involve in some respects a considerable departure from those usually employed in bacteriological research, for methods of examination based chiefly upon the isolation of organisms in pure culture do not provide us with the necessary information. As a systematic method of procedure, the plate method is inadequate. In the first place any solid medium is far too selective. In the second place, even if we were able to find a medium which would do justice to all the organisms and would faithfully reproduce all the flora of the intestine, we should be little if at all better off. Who is to say which organism is important and which is unimportant—which organism is directly concerned with the pathogenic condition and which is merely incidental? In certain cases the isolation of one or more organisms may be necessary or advisable but as a systematic method of investigation with regard to the bacteriology of the alimentary canal, the plate method must be put out of court as impracticable, since it fails to meet the essential requirements.

## TECHNIC

In the examination of the intestinal dejections the routine technic is as follows:

The "square" containing the dejection is removed from the infant, folded up, labelled and transferred at once from the ward to the research laboratory. In private cases the nurse is instructed to select a representative portion of the dejection, to place it in a closed vessel under suitable precautions and send it to the laboratory.

By means of a platinum loop a film is made on a glass slide (not a cover slip). The film is dried and fixed over the Bunsen, care being taken not to overheat the specimen. (In some cases, in which it is important to avoid any question of distortion by drying, the specimen is fixed by formaldehyd solution and alcohol, but this is not usually necessary.) The two routine staining methods employed are the Loeffler's blue method and a special method of staining devised by myself in which the Gram method is used with Loeffler's blue as a differential stain. As a rule cover slips are not used, the immersion oil being placed directly on the stained film. Should it be desired to preserve the slide, the oil is removed by zylol and the cover slip applied with Canada balsam in the usual manner.

The film is treated with Loeffler's blue for some thirty seconds, is washed and dried and is then ready for examination. This stain is especially valuable in revealing the structural details of the various organisms. The diplococci and the streptococci are stained a deep blue tending to violet, the lactic bacilli assume various shades of blue, while any granules they may contain are stained a brilliant red. The structure of the *Oidium lactis*, mycelia and spores, is very delicately shown. For all purposes of definition of structure Loeffler's blue is much to be preferred to gentian violet or the Gram stain as by these latter the finer structure is much obscured owing to the organisms being loaded with stain. As a matter of routine, I systematically examine the "Gram" film first, only resorting to the "Loeffler's blue" film when some question of structure requires elucidation.

To obtain good results with the Gram stain as applied to dejections some practical experience is necessary. The film is stained for two minutes with anilin

gentian violet. The stain is then poured off the slide and, without washing, the slide is flooded with the iodin solution. This solution is then poured off and a fresh quantity is poured on the film. This is then allowed to act for about thirty seconds. The solution is poured off and the slide is thoroughly washed. The film is then decolorized with 95 per cent. alcohol, care being taken that while the thin portions of the film are decolorized the denser portions are not, otherwise the film will be over-decolorized. After washing and drying the film is counterstained with Loeffler's blue.

The great value of this method is that it differentiates all the lactic group from the colon group. The *Streptococcus lacticus*, the *Bacillus lacticus* and the *Oidium lactis* (mycelia and spores) are all Gram-positive, while the colon bacilli are all Gram-negative, so that the lactic organisms are stained a deep purple, the colon bacilli a light blue (Fig. 22). Many organisms are Gram-positive besides the lactic organisms, notably the subtilis group, but these are not found in any number and they can be differentiated by Loeffler's blue and by culture methods described later. In practice it will be found that the incidental organs do not give rise to any serious difficulty.

The normal dejection contains numerous lactic bacilli, some colon bacilli and, possibly, a few diplococci (*Streptococcus lacticus*). As a rule diplococci are not seen or are inconspicuous for they are generally confined to the small intestine. This confinement of the streptococcus in normal conditions to the small intestine has been amply demonstrated in my laboratory, for in many cases in which cultures of the streptococcus have been administered for so long as a month, examination of the film has only resulted in finding a few isolated diplococci; the organism, however, grows freely when a portion of the dejection is transferred to sterilized milk.

In some cases the lactic bacilli are seen to be extremely active and to be greatly preponderant. They may be present in two forms—with or without granules. When granules are a pronounced feature, this indicates great activity. Both Kendall[3] and Finkelstein have drawn attention to the great tendency of these organisms to be found in certain cases "in almost pure culture." This observation has been abundantly confirmed by my own observations; indeed, I have many preparations demonstrating this feature.

In other cases, masses of diplococci or streptococci are seen, and these may be combined with lactic bacilli. In all cases in which the lactic organisms preponderate there will be a tendency to the exclusion of all other forms, while when violent purging occurs the tendency will be for the diplococci to be more and more exclusively represented, since in these circumstances it will be the contents of the small intestine that are in evidence.

3. Kendall: Observations on Aciduric (Acidophilic) Bacteria, Jour. Med. Research, February, 1910.

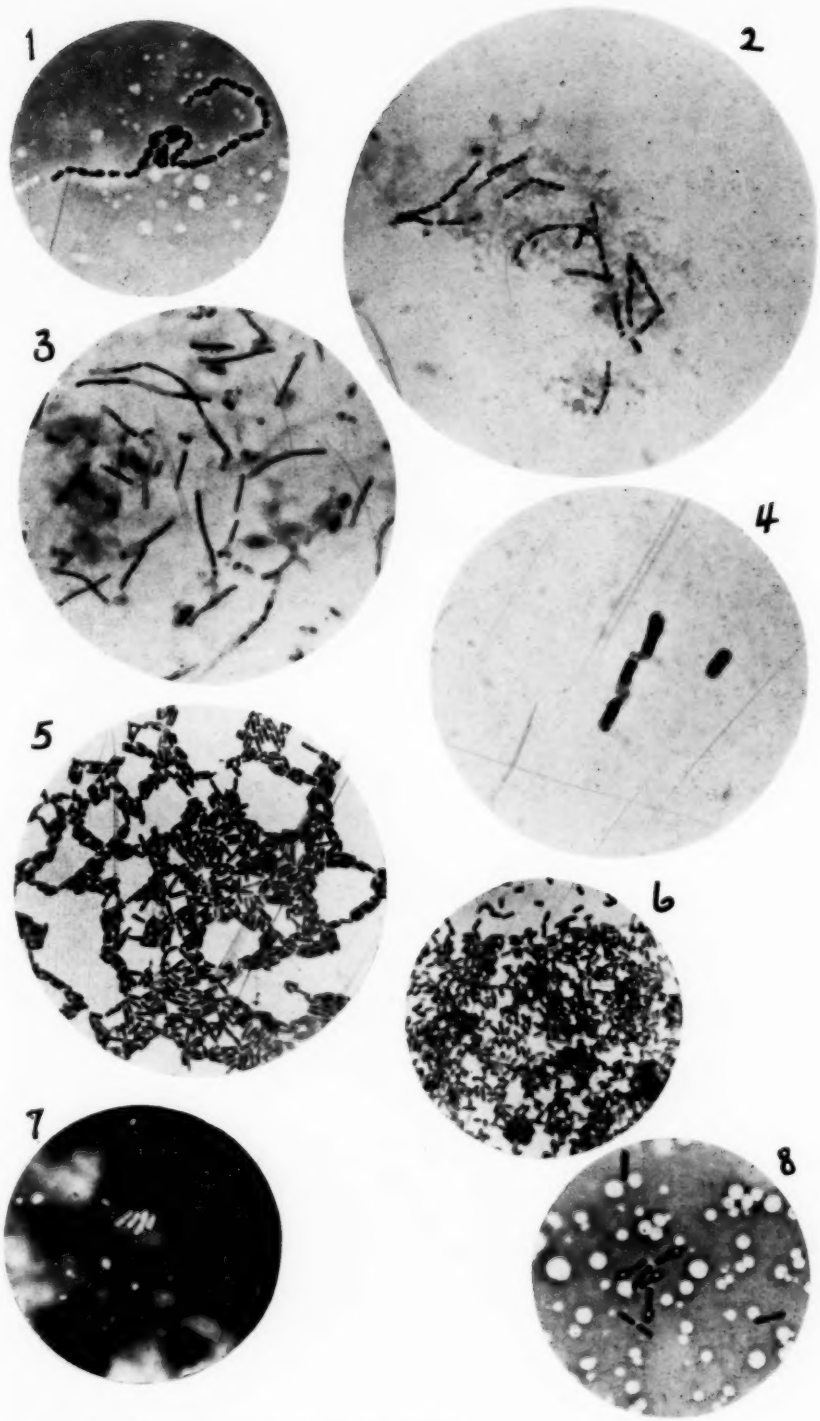


Fig. 1.—*Streptococcus lacticus* (× 1,000).

Fig. 2.—*Bacillus lacticus* (× 1,000).

Fig. 3.—*Bacillus lacticus* growing in milk incubated some days at 38 C. (× 1,000).

Fig. 4.—*Bacillus acidi lactici* (× 2,000).

Fig. 5.—*Bacillus acidi lactici* in peptone broth twenty-four hours at 38 C. (× 1,000).

Fig. 6.—*Bacillus coli* twenty-four hours in peptone broth at 38 C. (× 1,000).

Fig. 7.—Unstained colour organisms growing in raw milk at 19 C. (× 1,000).

Fig. 8.—*Bacillus putrificus* (× 1,000).

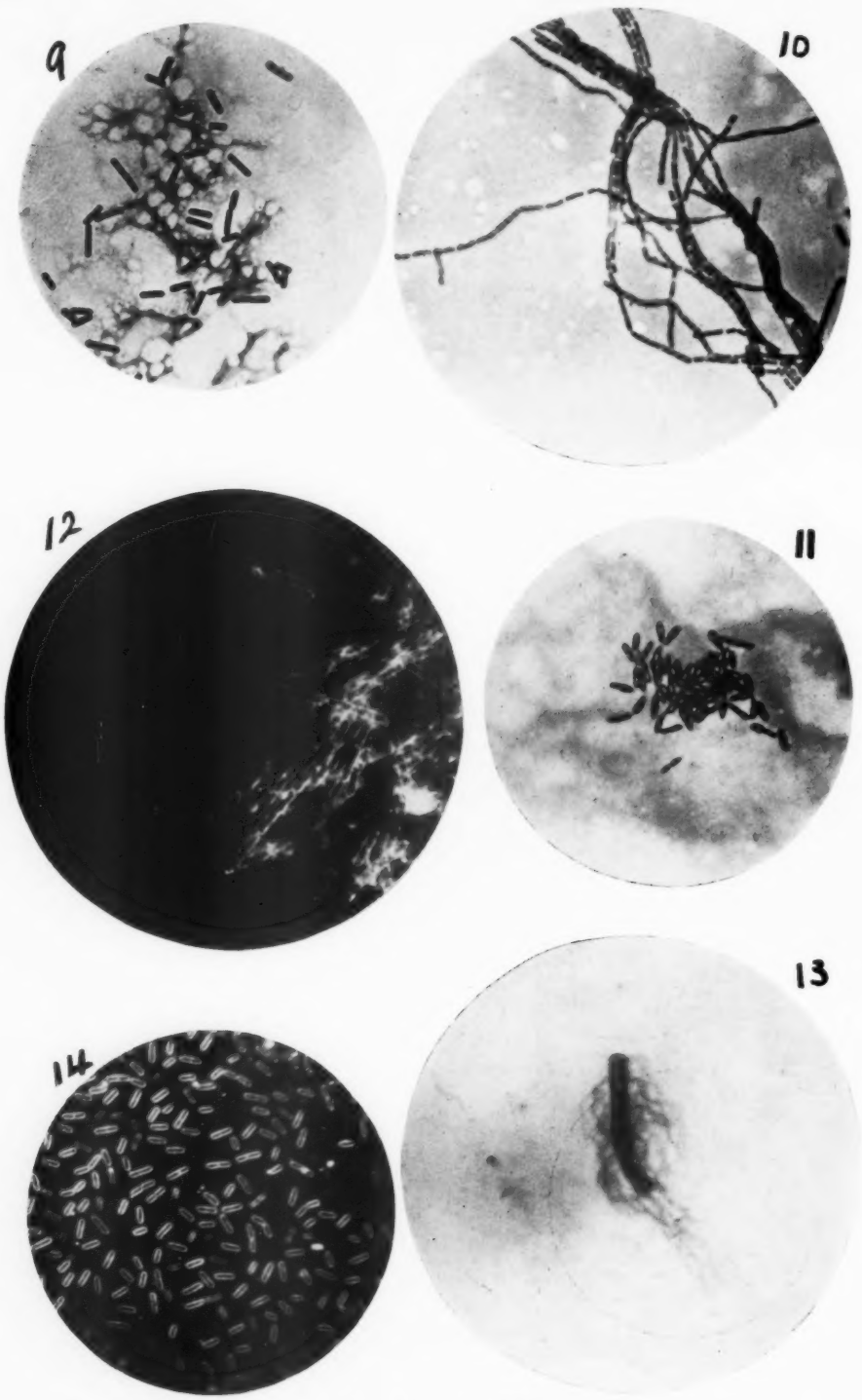


Fig. 9.—*Bacillus aërogenes capsulatus* (× 1,000).

Fig. 10.—Putrefactive bacteria growing in milk after it had been boiled (× 1,000).

Fig. 11.—Spores of putrefactive bacteria developing in milk after it had been boiled (× 1,000).

Fig. 12.—*Bacillus subtilis* in peptone broth (× 1,000), taken during life.

Fig. 13.—*Bacillus subtilis* showing flagella (× 2,000).

Fig. 14.—*Bacillus mesentericus* in peptone broth (× 1,000), taken during life.

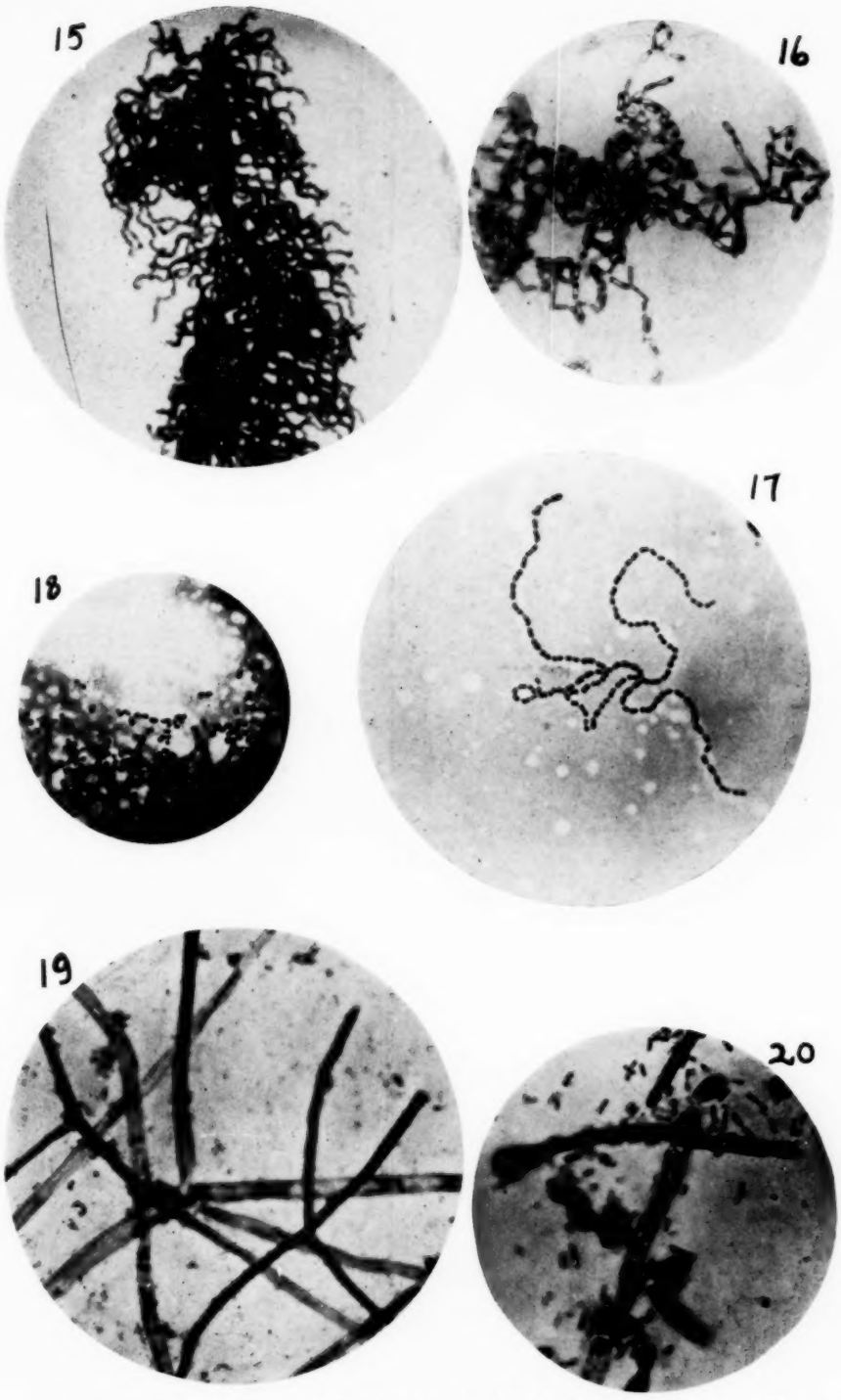


Fig. 15.—*Bacillus proteus vulgaris* with flagella (involution form) (× 2,000).

Fig. 16.—Spores of putrefactive bacteria in milk raised to 60 C. for twenty minutes and incubated for twenty-four hours at 38 C. (× 1,000).

Fig. 17.—*Streptococcus lacticus* as found in raw milk incubated for eight hours at 38 C. (× 1,000).

Fig. 18.—*Streptococcus lacticus*, twenty hours in sterilized milk at 38 C. (× 1,000).

Fig. 19.—Moulds growing in milk (× 500).

Fig. 20.—Moulds growing in milk (× 1,000).

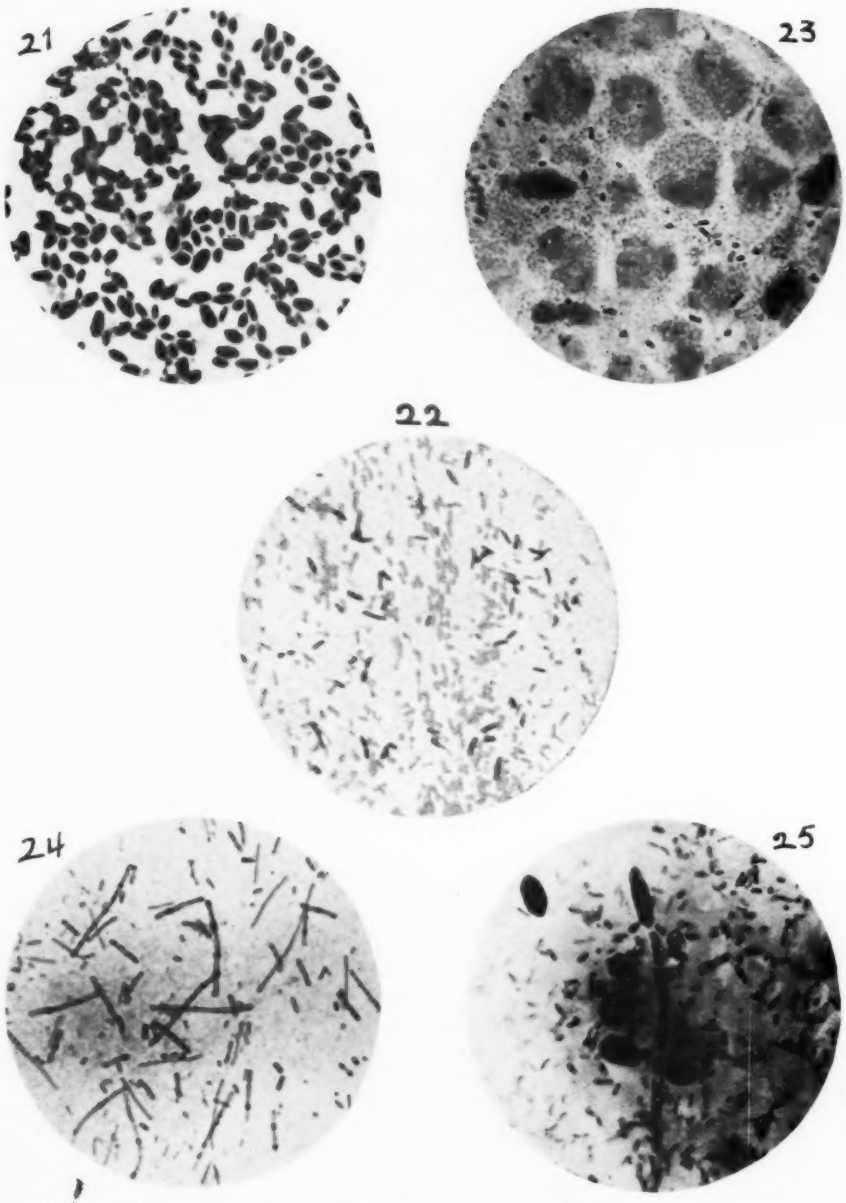


Fig. 21.—Yeasts growing in milk at 38 C. (× 1,000).

Fig. 22.—Color photomicrograph showing the colon organisms stained blue, the lactic organsms stained purple (× 1,000). (Case 13,231.)

Fig. 23.—Masses of large endothelial cells with Gram-positive diplococci (× 1,000). (Case 13,372.)

Fig. 24.—Masses of Gram-positive bacilli with well-marked metachromatic granules (× 1,000). (Case 13,049.)

Fig. 25.—Mycelium with conidia (× 1,000).

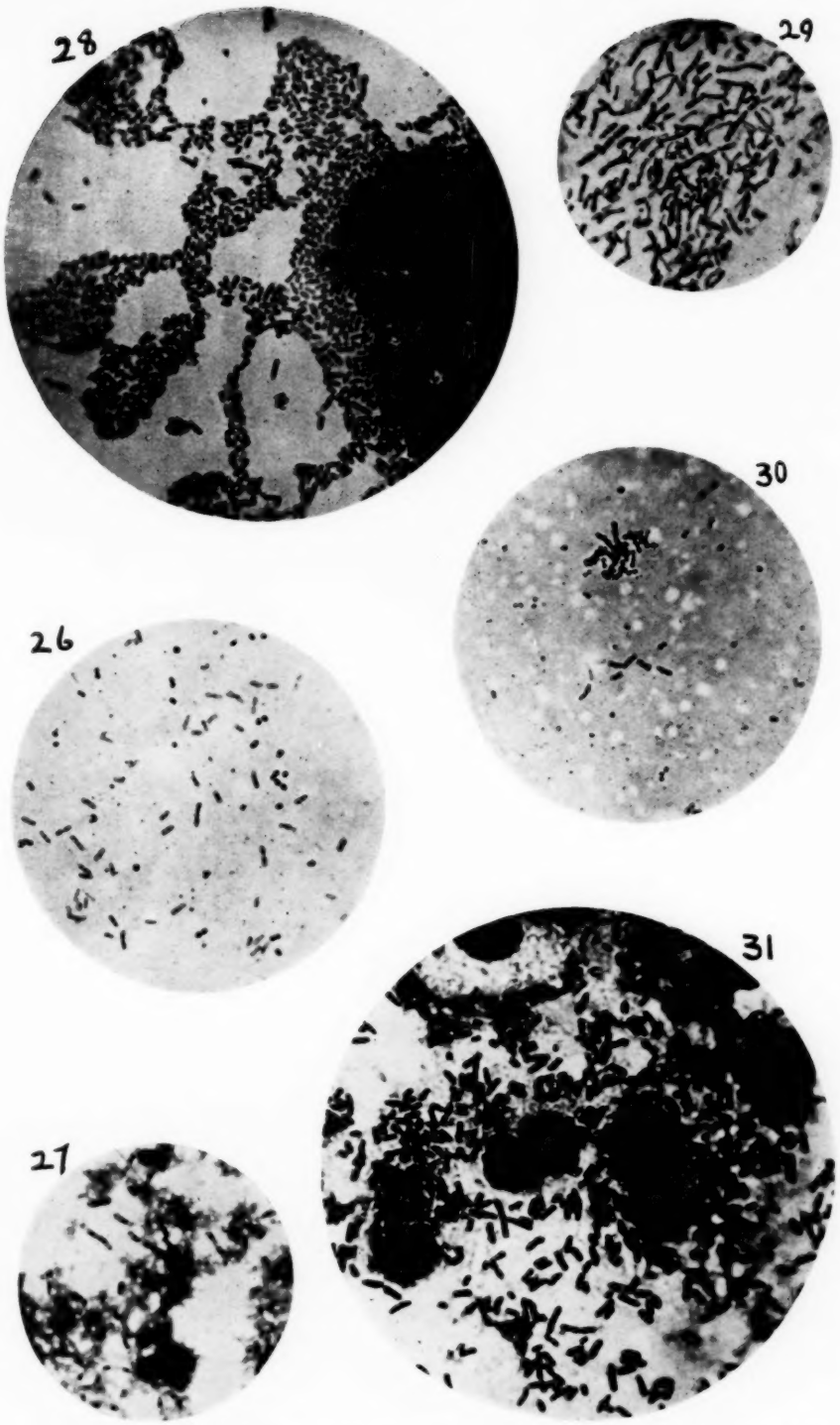


Fig. 26.—Culture in milk four hours at 38 C. Gram-positive diplococci and Gram-negative bacilli (× 1,000).

Fig. 27.—Culture in milk eight hours at 38 C. of colon bacilli with capsules (× 1,000).

Fig. 28.—Masses of colon organisms (× 1,000). (Case 10,270).

Fig. 29.—Same case as Fig 28, fourteen days later; numerous lactic bacilli, many with granules (× 1,000).

Fig. 30.—Culture in milk four hours at 38 C. Lactic bacilli above, colon organisms below (× 1,000).

Fig. 31.—Masses of Gram-negative bacilli with cells in urine (× 1,000). (Case 13,455.)

In other cases we may not infrequently find a mixed specimen, lactic organisms, colon bacilli, together with the *Oidium lactis,* or some allied fungus. All these are acid conditions and quite exclude a "colon toxemia." That in itself is a valuable indication, since we are in possession of definite information as to what should be done in the way of treatment, and, in particular, what should not be done.

### ACID POISONING—THRUSH

There are some cases of acid poisoning due to micro-organisms but they are very different from a colon toxemia. I refer especially to cases of "thrush." In one case the dejection was found to consist almost

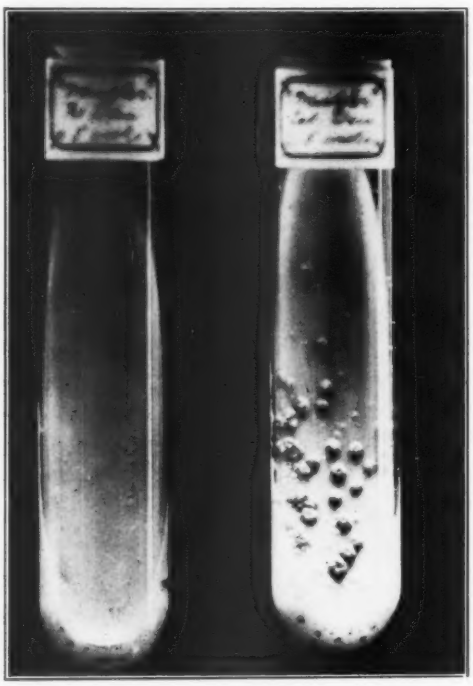

Figure 32. Figure 33.

Fig 32.—Growth of tubercle bacillus in medium without toxin.
Fig. 33.—Growth of tubercle bacillus in medium with toxin.

entirely of the spores of the *Oidium lactis* to the practical exclusion of all other organisms. I went to the ward and found an infant who had only been admitted a few hours previously. It was moribund and the mouth was covered with thrush. The infant, in fact, was "mouldy" from one end to the other. These moulds only develop in an acid medium and they may be compared with the rank vegetation found in acid marsh land. Fresh milk is extremely hostile to such fungi. As a

rule fresh milk will completely rid the intestine of the *Oidium lactis* in about twenty-four hours. A cooked milk containing an excessive amount of sugar of the wrong character is, according to my experience, the diet favoring the development of these organisms. They are, consequently, extremely liable to develop on a diet of condensed milk.

The *Oidium lactis* and the yeasts are organisms which grow luxuriously at blood temperature and they grow very feebly or not at all when the temperature is lower than 80 F. The moulds growing in milk at warm room temperature are inhibited by temperatures as high as that of the blood, but in other respects they are closely related to the *Oidium lactis;* they only grow in an acid medium. This can be readily realized by observing milk that has stood for some days at warm room temperature, for the moulds will form a thick "felt" on the surface of the milk. Their structure is best studied in a film stained with Loeffler's blue. It is advisable to study these organisms microscopically, as these examinations will greatly help the observer in regard to the recognition of mycelia found in the intestinal dejecta.

A marked and persistent dominance of the lactic organisms and particularly of the diplococci and streptococci is significant. In many cases a characteristic feature is the constitutional weakness of the infant. They are essentially "poor material." The intestine cannot endure the normal stimulus and the exaggerated peristalsis results in an abnormally rapid passage of the contents through the alimentary canal so that the control exercised by the colon is partially or completely abolished.

There are other cases which occasionally exhibit this acid dominance. An infant the subject of a grave disease, such as tuberculosis, tends by reason of its weakness to suffer from this condition. A case of colon toxemia treated with cultures of lactic organisms may suddenly "turn over" into a condition of acid dominance. This, however, should not happen if the dosage receives proper attention and the condition of the patient has been controlled by systematic examination of the dejections during the whole time the cultures are being administered. The condition may also develop in a child owing to the consumption of stale milk.

### COLON ORGANISMS

I have already drawn attention to the dual character of the colon organisms. They are facultative fermentative organisms but are eminently proteolytic when the conditions permit of this. In the normal conditions of the alimentary tract they must act fermentatively, for the acid contents of the small intestine prohibit the proteolytic phase while the diminishing acidity favors the fermentative action in the colon, for they are sensitive to acid and cannot act in the fully acid condition characteristic of the active growth of the *Streptococcus lacticus.* Thus the colon organisms can deal with remnants of lactose that may pass

the ileum producing thereby not only lactic acid but a small amount of gas. In some cases their fermentative action may be excessive with the result that much gas is produced and the infant suffers from colic and flatulence. This may especially be seen in cases where the young infant receives starchy food. According to my observations the administration of starch markedly encourages the growth of the colon organisms.

The microscopical features connected with the colon organisms relatively to the other organisms may now be discussed. In the normal dejection (Gram, counterstained Loeffler's blue) there are numerous lactic organisms while scattered throughout the field are colon bacilli stained light blue. The colon organisms are not massed together. The lactic organisms strike the eye, the colon bacilli are subservient. As the colon bacilli become more dominant the picture is altered. The lactic bacilli do not form a striking feature while a remarkable change is seen in the colon organisms. They occur in masses or streaks and their microscopical appearance is very different from that of the other organisms. The lactic bacilli are definitely seen to have three dimensions, length, breadth and depth (or roundness). The colon organisms appear to lack all depth. They lie flat and squat on the glass slide. A remarkable feature is that they are always *below* the lactic bacilli when these latter are present. I do not remember ever seeing a specimen showing the colon organisms above and the lactic organisms below. An excessive number of colon bacilli is a bad feature, for it means that the controlling organisms are failing. Since the colon organisms can only achieve dominance by the suppression of the lactic organisms their excessive number even when they are acting fermentatively must be regarded as a stage towards their proteolytic development, for proteolysis by the colon organisms in the intestine cannot occur suddenly; it can only occur as a late result of prolonged abnormality.

As the colon organisms become proteolytic the microscopical picture alters. They are less sharply defined, their outlines are blurred and they are very pleomorphic. With Loeffler's blue they stain vaguely and some assume a dirty yellowish tint. Sometimes with the Gram method and counter-stain of Loeffler's blue the colon bacilli are better stained than they are when treated with Loeffler's solution alone. This is due to the mordant action of the anilin oil, and the difference of staining as regards the colon organisms by the two methods is worth noting, since it indicates proteolysis. In some cases the capsular attachments of the colon organisms are very distinct. This is as a rule a bad feature since it generally indicates virulence.

Some considerable practical experience is necessary to enable the observer readily to pick up the leading indications presented by the specimens, but it will be found that the majority of the cases are fairly

straightforward, while in the others some special factor has to be taken into consideration, and as these are brought into line as the result of more extended investigations, they generally prove to be extremely valuable in elucidating the special features of the particular case.

### VALUE OF BACTERIOLOGICAL DIAGNOSIS

Among the workers at The Infants Hospital there is no doubt that by means of the bacteriological examination we have arrived at a means of diagnosis which in respect of accuracy and precision is far superior to any other means at our disposal. Our diagnosis and treatment are fundamentally dependent on the reports from the Research Laboratory. This has really been established beyond doubt by the close correspondence between the gravity of the bacteriological report and the gravity of the clinical condition. This is so important that I may very briefly refer to the kind of evidence that has impressed us. It was only the other day that I proceeded directly from the laboratory to the wards in order that while the microscopical picture was still in my mind's eye I might immediately correlate it with the actual clinical condition, for the appearances indicated a very grave condition. The infant was dead. It had only been admitted the previous afternoon and died the same evening. On one occasion my report indicated a severe colon toxemia. On my proceeding to the cot it was clear that there had been some mistake. I insisted that this infant had never passed the dejection reported on, and, in order to establish this, gave instructions that the next dejection from this infant should be sent to the laboratory. A minute or two later the sister of the lower ward came to the laboratory to report that a mistake had in fact been made. The cot was No. 18, but it was No. 18 in the upper ward. We immediately proceeded to this ward and there found the infant. It was comatose. This incident occurred some time ago, but it demonstrated to us all in a striking manner the fact that the personal equation had been sufficiently eliminated and that only practical experience was required to enable the observer definitely to recognize by bacteriological examination the character of the case.

While the direct microscopical examination is most important and should never be omitted, it is not solely relied on. For the complete examination we require to determine the organisms that are dominant, by observing which of them appear when a portion of the dejection is transferred by means of the platinum loop to sterilized milk. Milk is necessarily the chief culture medium systematically employed. Peptone broth is quite unsuitable, for the colon organisms grow rapidly in such a medium, while the lactic bacilli and the *Streptococcus lacticus* cannot grow at all. Obviously, any inference based on the growth of organisms in such circumstances would be highly fallacious. At the same time there are cases in which peptone broth may be usefully employed, but it

can only be of service when the growth in this medium is compared with the growth in milk.

Milk tends to favor the growth of the normal lactic organisms, so that if these are present in proper proportions and number they should soon appear in the milk culture. Some difficulty may be found with reference to the streptococci. A ready growth occurs, for example, in milk in eight hours. This indicates the fermentative type, but it is found that, in an eight- or twelve-hour culture in peptone broth some short chains of diplococci are present. These organisms are not *Streptococcus lacticus*. They are probably, like the *Bacillus subtilis*, merely incidental and belong to the type *Streptococcus saprophyticus*. We have recently isolated a coccus which is known in the laboratory as "No. 77." This is a proteolytic coccus and is Gram positive. It can grow to some extent in milk, but grows much more freely in peptone broth. As a rule, it is not difficult to distinguish it morphologically from the *Streptococcus lacticus*. When growing as a diplococcus it is bulkier and is frequently found in the staphylococcic form. Other considerations need to be borne in mind. What is the character of the other organisms? It would not be consistent to specify a culture as containing numerous lactic bacilli and numerous proteolytic streptococci. It should also be remembered that a real dominance of the obligate proteolytic organisms in the intestine is not consistent with a living child. Such absolute putrefaction as this implies could only occur in a dead body. On the question of the relationship of the proteolytic streptococci to alimentary disease I have not been able to arrive at any definite conclusion. In some cases we have to deal with streptococci, which are both fermentative and proteolytic, according to the conditions of the medium; in these cases they need to be grouped with the colon organisms. But in the large series of cases examined I have not been able to attribute any serious conditions to the presence of proteolytic streptococci. In the cases in which I have found them and where they have grown readily in peptone broth the infants have not been seriously ill. As a rule, they have been suffering from a mild colon toxemia. While the milk medium is favorable to the development of the lactic organisms, it is not so unfavorable to the colon organisms that they are unable to grow. In the presence of numerous and active lactic organisms they would be speedily dominated and inhibited; but in the absence of such dominance the medium does not offer difficulty to the coliform bacilli, though not by any means the best medium for their development. Hence their development in such a medium demonstrates their dominance, especially if they persist at stages of incubation when in normal circumstances their growth should have been inhibited.

My investigations in regard to the biochemical changes occurring in raw milk had taught me that in all such inquiries the usual periods of

bacteriological incubation were much too long. In twenty-four hours nearly everything that the cultures have to tell us has been obliterated, and consequently we systematically investigate the conditions as found in the milk cultures at 38 C. after four hours' and after eight hours' incubation, only prolonging our investigation at twelve hours' incubation or longer when this appears to be indicated. This investigation does not tell us how many varieties of bacteria are in the intestinal canal. It, indeed, omits much, for it leaves out the unessential and the incidental and consequently brings into prominence the cardinal facts. What are the organisms that are in action in the alimentary canal, and what is their character? By observing the nature of the organisms, the order of their appearance and their relative dominance, we are able to obtain a real conception of the processes occurring in the alimentary canal. Moreover, as the case proceeds, we are in a position accurately to appraise the changing conditions, and I have selected a number of typical reports in order to demonstrate the methods by means of which the diagnosis is made. The various organisms found in the dejections and cultures are illustrated by the photomicrographs (Figs. 22 to 33).

REPORT 13,287.—Many Gram-positive bacilli. Gram-positive diplococci very little in evidence. A few Gram-negative bacilli.

In milk four hours. Gram-positive diplococci very numerous, a few Gram-positive bacilli. Very few Gram-negative bacilli.

In milk eight hours. Milk curdled, not gas blown. Masses of Gram-positive diplococci, some in chains of three or four units. Very few Gram-positive bacilli. Very few Gram-negative bacilli.

No evidence of abnormality. The *Streptococcus lacticus* is very active, as shown by the number of diplococci in the four-hour culture and by the curdling of the milk in the eight-hour. If there were diarrhea it would be well to reduce the lactose and take other steps to restrain the activity of the lactic organisms, but this should not be done unless the clinical condition indicates this. The report absolutely excludes alimentary toxemia.

REPORT 13,175.—Mycelia distributed throughout the specimen, many with spores. Some Gram-positive bacilli. Some Gram-positive diplococci.

In milk four hours. Gram-positive diplococci numerous. Some Gram-negative bacilli. Some Gram-positive bacilli; with Loeffler's blue some of these show red granules.

In milk eight hours. Milk curdled and gas blown. Many Gram-positive diplococci. Many Gram-negative bacilli, a good many being rather degenerated.

The mycelia indicate a rank condition. This is a case which might readily proceed to a marked colon toxemia, but this is, however, some way from being established. Although the natural organisms are still acting in the greater part of the small intestine, the presence of mycelia indicates that they are far from dominant. The case should rapidly respond to proper dietetic treatment.

REPORT 13,214.—Gram-negative bacilli very numerous. Many Gram-positive bacilli. Very few Gram-positive diplococci.

In milk four hours. Numerous Gram-negative bacilli. No other organisms seen.

In milk eight hours. Gram-negative bacilli extremely numerous, large numbers being found in each field. A very few Gram-positive diplococci.

A clear case of colon toxemia.

REPORT 13,231.—Masses of Gram-negative bacilli. Some Gram-positive bacilli. (Fig. 22.) A few mycelia.

In milk four hours. Many Gram-negative bacilli. Some Gram-positive bacilli. Some of these latter show red granules with Loeffler's blue.

In milk eight hours. Numerous Gram-negative bacilli. Some Gram-positive bacilli. Some Gram-positive streptococci.

The masses of Gram-negative bacilli in the dejection and their persistence in the cultures indicates a definite colon toxemia.

REPORT 13,260.—Many spores of a fungus of *Oidium Lactis* type. Some Gram-positive diplococci. Some Gram-negative bacilli.

In milk four hours. A few Gram-negative bacilli. No other organisms seen.

In milk eight hours. Masses of Gram-positive diplococci. A few Gram-positive bacilli. A few isolated Gram-negative bacilli.

A similar case is 13,175. If kept on a cooked milk this case would probably develop into a case of colon toxemia; but the infant should rapidly respond to treatment, for the *Streptococcus lacticus* is well represented, as shown by the eight-hour culture.

The *Oidium lactis* will rapidly disappear on a diet of raw milk.

REPORT 13,272.—Masses of small Gram-negative bacilli. Some Gram-positive bacilli. A few gram-positive diplococci.

In milk four hours. Numerous Gram-negative bacilli. Some Gram-positive bacilli and diplococci.

In milk eight hours. Milk curdled and gas blown. Large numbers of Gram-negative bacilli. Some Gram-positive streptococci and bacilli.

The effect of a raw milk diet is seen in the report a week later.

Masses of Gram-positive diplococci, very few Gram-negative bacilli.

In milk four hours. Some Gram-positive bacilli and diplococci. No Gram-negative bacilli seen.

In milk eight hours. Masses of Gram-positive diplococci. Some Gram-positive bacilli. No Gram-negative bacilli seen.

The child was 14 months of age and weighed 9½ pounds. It was stated to have weighed 9 pounds at birth. It had been fed on every variety of food.

These infants generally show an intolerance of the natural diet and of the natural stimulus of a normal amount of acid, owing to the atrophied and weakened condition of the intestine. The latter report indicated that there was danger of an acid diarrhea developing, for masses of diplococci ought not to be seen in the dejection and consequently lactose was reduced to the *minimum*, while casein was given in considerable amount.

REPORT 13,290.—Masses of Gram-positive bacilli. Some Gram-negative bacilli. No diplococci seen.

In milk four hours. Masses of Gram-negative bacilli. Some Gram-positive bacilli. No diplococci seen.

In milk eight hours. Masses of Gram-negative bacilli; many showing capsules. Some differentiated Gram-positive bacilli. No diplococci seen.

In milk forty-eight hours. Masses of Gram-positive bacilli. Some degenerated Gram-negative bacilli. No diplococci seen.

Eight days later: Numerous Gram-positive bacilli and diplococci. Very few Gram-negative bacilli.

In milk four hours. Numerous Gram-negative bacilli. Some Gram-positive diplococci.

In milk eight hours. Masses of Gram-positive diplococci. A few Gram-positive bacilli. A few Gram-negative bacilli.

Coupled with the activity of the colon organisms, the absence of diplococci in the cultures was a bad sign. The absence of these was so striking that incubation was prolonged to forty-eight hours without obtaining any evidence of the *Streptococcus lacticus*. The later report shows the change in the condition.

REPORT 13,389.—Many Gram-positive diplococci and streptococci. Many Gram-positive bacilli. Some *Oidium lactis*, mycelia and spores. Gram-negative bacilli fairly numerous.

In milk four hours. Some Gram-positive diplococci. Some in small chains. Some Gram-negative bacilli.

In milk eight hours. Gram-positive diplococci very numerous. Some in small chains. Gram-negative bacilli fairly numerous.

Abnormal but not seriously so. Raw milk is the treatment, but it will need to be modified so as to contain only a small amount of lactose at first; otherwise an acid diarrhea would probably develop.

REPORT 13,303.—Masses of Gram-positive diplococci; no other organisms seen.

In milk four hours. No organisms seen.

In milk eight hours. Numerous Gram-positive diplococci. Some in small chains. No other organisms seen.

A superdominance of the *Streptococcus lacticus*. Indicates a lienteric diarrhea; if in a young infant probably some degree of constitutional weakness. The absence of organisms in the four-hour culture is rather striking; the same feature is characteristic of a raw milk, which in about eight hours will be crowded with streptococci.

REPORT 13,372.—Masses of large endothelial cells. (Fig. 23.) Numerous Gram-positive bacilli and diplococci. Gram-negative bacilli few.

In milk four hours. Numerous Gram-positive diplococci. Some in small chains. Some Gram-negative bacilli.

In milk eight hours. Gram-positive diplococci; some in small chains. Some Gram-negative bacilli.

In milk eight hours. Gram-positive diplococci very numerous, many being in small chains. Many Gram-negative bacilli.

The irritant condition that this report implies is almost invariably associated with an acid condition. As a rule, the organisms producing

toxemia do not produce irritant effects on the intestinal mucous membrane. In this case the dejection was blood-stained. In England involvement of the mucous membrane in diarrheal conditions in infants is distinctly rare. This statement is based on the microscopical examination of many thousands of consecutive cases. In America it would appear that the mucous membrane is more frequently involved, judging by the clinical reports in regard to the presence of hemorrhage. I am familiar with these conditions in children. Cases of acute colitis with free hemorrhage, caused by the *Bacillus aërogenes capsulatus,* are not uncommon, but I have never seen a case of this kind in a patient under 12 months of age.

REPORT 13,445.—Masses of Gram-negative bacilli. A few Gram-positive bacilli. Diplococci not in evidence.

In milk four hours. Some Gram-negative bacilli. One or two Gram-positive bacilli. No diplococci seen.

In milk eight hours. Masses of Gram-negative bacilli. A very few Gram-positive bacilli. No diplococci seen.

Specimen of Urine: Numerous Gram-negative bacilli. Many cells.

In deposit from centrifugalized specimen of urine were seen masses of Gram-negative bacilli and cells. (Fig. 35.)

A child of 18 months suffering from chronic colon toxemia. On this supervened acute illness in the shape of pyelitis, which was associated with a high temperature and rapid wasting. The child died a few days after admission.

REPORT 13,255.—Many Gram-positive diplococci. Numerous Gram-negative bacilli. A few Gram-positive bacilli.

In milk four hours. Numerous Gram-positive diplococci; some Gram-negative bacilli. A few Gram-positive bacilli.

In milk eight hours. Masses of Gram-positive diplococci; some in chains. No other organisms seen.

In peptone broth eight hours. Numerous Gram-positive diplococci. A few Gram-negative bacilli.

In peptone broth twenty-four hours. Very numerous Gram-negative bacilli. Many long threads of *B. mesentericus vulgatus* type. Some Gram-positive streptococci.

While some of the diplococci may be of the *Streptococcus lacticus* type, it is clear that others are not, and that we have to deal here with a proteolytic streptococcus. The activity of this organism is shown by its marked dominance in the eight-hour peptone-broth culture. In the twenty-four-hour culture the colon organisms and the *B. mesentericus vulgatus* are dominant.

REPORT 13,049.—Masses of long Gram-positive bacilli. Some Gram-positive diplococci. No Gram-negative bacilli. Stained with Loeffler's blue the bacilli contain numerous well-marked red granules. (Fig. 24.)

In milk four hours. Some Gram-positive bacilli with granules. Some Gram-positive diplococci.

In milk eight hours. Numerous Gram-positive bacilli with granules. Some Gram-positive diplococci.

An acid diarrhea occurring in a child that died of generalized tuberculosis.

It will be obvious that, quite apart from specific treatment, the bacteriological diagnosis influences our whole conduct of the case. Even where specific treatment is not called for the knowledge of the nature of the case determines our whole attitude towards it. As an example I may mention the case of the child, 13,049, who was evidently very ill. The symptoms were obscure, but the drowsiness and other symptoms pointed to a colon toxemia as a possible explanation of the condition. The bacteriological report immediately put this out of court, for the lactic organisms were extremely dominant. At the post-mortem examination we found one feature of interest in the present connection. The contents of the small intestine were strongly acid, but at the ileocecal valve there was a marked change and the contents of the large intestine were amphoteric.

In dealing with an intestinal condition due to dominance of the acid-forming organisms, the first line of treatment is the exclusion of all diet calculated to assist the lactic organisms. Raw milk must be forbidden. Cooked milk with the lactose reduced to a minimum amount is indicated. In such cases we may give a reasonable amount of fat and a considerable amount of protein in the shape of caseinogen. If this be given in the shape of milk the lactose may still be too much, and we may therefore employ a precipitated casein. In these cases chalk may be useful in contending with the excessive acid, and opium in minute amounts in the case of the young infant may be useful in calming the irritated intestine. So that some very old-fashioned remedies are found to have their justification in the bacteriological condition of the intestine.

A favorite preliminary treatment in these cases at The Infants Hospital is albumin water made with normal saline, which we term "saline albumin." With this are combined a few teaspoonfuls of a diluted meat extract, while small doses of brandy are given at intervals. Opium is also given in small doses. Very gradually a normal milk diet is introduced, but throughout the treatment the dietetic and medicinal treatment is constantly checked by examination of the dejections. In this class of case it would appear that we have tended to exaggerate the value of purgation. Active stopping of the diarrhea is not unsound. To stop the excessive acid production and give rest to the irritated intestine are the immediate indications.

The precise treatment of the conditions arising from dominance of the colon organisms depends a great deal on the age of the infant. In the young infant—under 6 months, and particularly under 4 months—the intestinal conditions are rather apt to undergo very rapid changes.

In a moderate case of colon toxemia where the constitutional symptoms are not severe, it is a mistake to undertake too active treatment with a view to the rapid suppression of the dominant organisms. Such rapid changes are likely to prove extremely disturbing, for the young infant cannot tolerate alimentary revolution. Even raw milk may be too sudden a change from the wrong diet it has been receiving, and it may be necessary only gradually to introduce the natural diet. As a rule treatment with cultures of the lactic organism is not indicated. It is better to adopt measures favoring the gradual development of the lactic organisms by dietetic management than by the administration of pure cultures. If the case is obstinate and the colon dominance persists despite the administration of raw milk containing a good proportion of lactose, then the administration of cultures is indicated.

The worst instances of acute intestinal toxemia are, in my experience, only seen in hospital cases. The infants may suffer from diarrhea, but in the extreme type there is constipation. The result is nearly always fatal. These are the true cases of intestinal toxemia and are caused by the action of the proteolytic organisms. According to my observations this class of case never occurs unless the infant has been fed on cooked food, or there has been in other respects some extreme departure from a natural diet.

It is well known that bronchopneumonia is extremely apt to develop in infants suffering from intestinal affections. Frequently after the infant has more or less recovered from the acute stage of the bronchopneumonia, it again becomes seriously ill and not infrequently dies. These cases are generally cases of colon toxemia supervening on bronchopneumonia. The swallowing of the mucus is largely responsible for this, since it provides an almost ideal diet for the colon organisms and consequently in cases of bronchopneumonia the dejections should be systematically examined so that, on the appearance of any colon dominance, cultures of the *Streptococcus lacticus* may be immediately administered.

Colon toxemia exerts a profound influence on the general health. It is not merely a question of lessening the power of resistance, for it has been shown experimentally that certain organisms, notably the tubercle bacillus, will grow in the culture tube much more actively and much more rapidly in the presence of bacterial toxins than they will in their absence. When the tubercle bacillus is grown in a medium with and without toxin it is found in some cases that the growth of the cultures is very greatly accelerated by the presence of the toxin in the medium. The acceleration so produced may result in a growth a million times greater than the growth in the medium without toxin.[4] (Figs. 32 and 33.)

4. Allen: Bacterial Diseases of Respiration, London, 1913.

According to my observations, children fed on boiled milk are more liable to contract tuberculosis, and especially the more serious forms of tuberculosis, than children fed on raw milk, and I believe the reason for this is the chronic toxemia resulting from the proteolytic action of the colon bacilli.

Whereas treatment by cultures of the antagonistic organisms is not, as a rule, indicated in young infants, in older infants and in children I have in the last few years obtained the most gratifying results by bacteriological treatment.

In some of the cases there has been a history of an acute illness followed by chronic ill health; in others no history of acute illness can be obtained. In order to illustrate the character of the symptoms and the somewhat protean form that they may take, I cite three cases, omitting everything but the essential details.

### CASES ILLUSTRATING BACTERIOLOGICAL TREATMENT

CASE 1.—A girl aged 10 years. In very poor health. Very anemic. Suffers severely from headache and vomiting, the symptoms generally being those of "migraine." In the previous twelve months school work had to be abandoned. Catarrh of practically all the mucous membranes. In particular the bronchial catarrh was so marked that the expiratory murmur was much louder than the inspiratory. The bacteriological examination showed a pronounced colon toxemia.

The diet ordered consisted largely of milk. One meat meal a day was allowed. Milk puddings and all forms of cooked milk were forbidden. Cultures of the *Streptococcus lacticus* were given four times a day.

At the end of ten days the bronchial catarrh had completely disappeared and all the symptoms were greatly improved. After a month's treatment the cultures were suspended, the diet remaining unaltered. In rather less than a fortnight the symptoms began to return. They rapidly disappeared on the cultures being again administered. These were persevered with and in three months she seemed to be fully recovered. The cultures were then suspended. In three weeks symptoms of headache and malaise appeared. Cultures were again given with immediately beneficial results, and they were continued for a further three months. She then did well without the cultures and continued in good health for nearly two years.

CASE 2.—A boy aged 5 years. Severe attack of vomiting at intervals ranging from about three weeks to three months. These vomiting attacks lasted as a rule for about three days — never less than forty-eight hours — and during this time everything was vomited. At the end of these attacks he was very weak but soon picked up and in the intervals was apparently in good health. He had a distinct tendency to constipation and aperients had to be given rather frequently. He always needed to be dieted very rigidly, otherwise he soon became ill; but on the most rigid diet the attacks could not be prevented.

The examination showed an extreme dominance of colon organisms but it appeared to be probable that the symptoms were caused by carbohydrate fermentation in the small intestine by the colon organisms. This opinion was based on (1) the excessive gas production in the milk culture; (2) the clinical condition: a proteolytic toxemia was hardly consistent with the good health in the intervals between the attacks.

Raw milk was made the predominant element of diet and cultures of the *Bacillus lacticus* and the *Streptococcus lacticus* were given four times a day. The cultures were given systematically for six months. During this period he had no

attack. After two months suspension of the cultures he had a slight attack of vomiting, but it lasted less than twelve hours. He then received a further three months bacteriological treatment, and he has now been for over a year quite free from any attack.

CASE 3.—A girl aged 3 years. Enlarged spleen. Enlarged liver. Pronounced anemia. No appetite; systematically refuses food. Great languor and weakness. Quite unable to walk and only able to stand while holding on to some support. She had been seen by many physicians and for some time the diagnosis had been "splenic anemia." It was a typical case of chronic colon toxemia. The child was ordered raw milk, with water and milk-sugar and cultures of the *Streptococcus lacticus* and *Bacillus lacticus*. In three days the child was hungry. She gradually made a complete recovery. On two occasions the cultures were suspended, the diet remaining the same, with the result that the symptoms began to recur in about ten days.

This case is peculiarly interesting for when the child had been in quite good health for over six months she began to relapse. A return of the symptoms is not uncommon when the cultures are suspended at too early a date. But the normal lactic organisms had evidently become well established and it was consequently difficult to account for the condition, especially as the mother insisted that she had strictly adhered to the diet as ordered. It was then ascertained that the family had come to town. Previously they were living in the country. The mother was at once asked where she obtained the milk. She replied by giving the name of a milk company that systematically pasteurizes all its milk, though it carefully conceals this fact from its customers.

It would be tedious to cite the details of further cases, especially as scarcely a week passés in which I do not see some new combination of symptoms due to alimentary toxemia. The above cases will, however, serve to illustrate the kind of case in which we may expect to find this condition and the principles governing their bacteriological treatment.

Certain points are of importance. The pure cultures are necessarily prepared in sterilized milk, but they are never given with cooked milk. This is a great mistake. Milk in its natural condition is the most favorable medium for the lactic organisms, and they exert their antitoxic action far more powerfully in this medium than they do when the milk is cooked.

The bacteriological examination should always be made by the physician. He must know at first hand everything about his case. The cultures must be prepared under his direction and control. Various strains of the *Streptococcus lacticus* and the *Bacillus lacticus,* either alone or in combination, are employed according to the precise indications. Some strains of the *Streptococcus lacticus* are more capable of maintaining themselves in action in the intestine than others, and this has to be considered not only in relation to the streptococcus, but also in relation to the toxic organisms. Some varieties of the *Bacillus lacticus* rapidly produce a large amount of acid. Other varieties grow slowly at first and do not come into action until the activity of the streptococcus has more or less ceased. All these considerations need to be taken into account in regard to the actual requirements of each case. Finally, it is essential that the cultures should not be administered unless the patient is under

observation and systematic bacteriological examination of the dejections can be made. It would be much better that the bacteriological treatment of intestinal conditions should be altogether neglected than that it should be carried out in a superficial and perfunctory manner.

In thus summarizing the results of my observations during the past few years, my chief object has been to deal with the principle underlying the methods applied and to so describe the actual procedures that they may be applied and tested. Almost every day some new factor comes to light which needs to be considered and correlated with the phenomena that have already been observed; but by the methods of investigation which have been discussed I have been enabled to get nearer to the solution of the problem than by any other method. If we are to deal scientifically with the pathogenesis of intestinal diseases we must check and control our clinical diagnosis, while in regard to treatment, all our efforts must be somewhat empirical unless we are in a position adequately to comprehend the nature of the biochemical processes which are responsible for the diseased conditions.

# PELLAGRA IN EARLY CHILDHOOD*

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Pellagra until recently was of historical interest only to the American student of medicine, who read of its prevalence among the peasantry of Southern Europe. We little suspected that this scourge was present in the United States; for although rare sporadic cases had previously been reported in this country, it was not till April, 1907, that Dr. G. H. Searcy, assisted by Drs. Dyer of New Orleans, Bondurant of Mobile, and McCafferty and Somerville of Mt. Vernon, Ala., reported to the meeting of the Alabama State Medical Association eighty-eight cases of pellagra as having recently been observed in the Mt. Vernon (Ala.) Asylum for Insane Negroes. This report constitutes a valuable contribution to the history of the disease in America, but did not receive the attention it deserved, as only one case was reported as a result. This was by Dr. T. C. Merrill of Texas.

In December, 1907, Dr. J. W. Babcock of Columbia, S. C., working in ignorance of Searcy's observations, reported to the South Carolina State Board of Health nine cases of pellagra from that state, mostly among the inmates of the State Hospital for the Insane. This report received wide publicity in both the medical and lay press and created wide-spread interest in many portions of the country. Following this publication, cases were reported from many sections of South Carolina and other states. Interest in the matter became so great that, early in 1908, the United States Public Health Service became active in the study of the situation. From the combined agencies at work in the last five years it is definitely known that the disease exists more or less extensively in many states, having now (1913) been reported from all except Montana, South Dakota, Nevada, Utah, Wyoming, New Hampshire and Delaware. It is difficult to understand its absence from at least some of these states, as its presence has been reported from states adjoining most of them, and it is probably a question of only a short time when it will be reported from all.

The disease is evidently not a new disease in America, Babcock having traced it back as far as 1834, and possibly to 1828, in the South Carolina State Hospital for the Insane. There was a case observed in Massachusetts in 1860, and reported, with one from New York, in 1864; and cases are known to have occurred in several other

*Read before the Lexington (S. C.) Medical Society, Oct. 8, 1913.

states from 1882 to 1889. The disease, then, has certainly been overlooked in our country, as it was in Egypt, but it is quite inconceivable that it has existed in the past to such a degree as it does now—from 30,000 to 50,000 cases being estimated for the United States; and so we are forced to the conclusion that, while the disease is seemingly spreading, our knowledge of it is increasing also. Every physician who sees cases must realize that at least some of the patients have had previous attacks which were not recognized. The fact that the disease has been present and not recognized cannot be taken as a reflection on only American physicians, as we have recently learned how the same thing happened in England after Box reported two cases in a family living near London. Following this report, more than fifty other cases have been reported, and Sambon says he thinks there are hundreds of cases in the British Isles. The same experience has been met with in regard to the slow recognition of pellagra in other countries, as Egypt, Austria and Roumania.

The physicians of America were entirely unprepared for the announcement that this disease was epidemic in many parts of the country, because no less an authority than Dr. Osler, in the 1907 edition of his Principles and Practice of Medicine, in the brief section on pellagra, asserts that it has not been observed in this country. Several years ago, before the disease had been recognized, a case of typical pellagra was presented for diagnosis to one of the most famous diagnosticians of Philadelphia. After examining the patient, he pronounced it glossitis. There are many instances of this kind where distinguished physicians, who were really astute observers, have mistaken pellagra for scurvy, eczema, various kinds of intestinal troubles, syphilis, and many other diseases, and recently in England for "ringworm."

That pellagra occurs in infants has been repeatedly denied, even in Italy. Odoardi, in 1776, says he has not seen it in boys or girls under 6 or 8 years of age. Soler, writing a few years later, says: "Children below the age of 12 are exempt." Strambio, the elder, however, writing about this time, says he has "observed the disease in sucklings." In regard to age, in Lavinder and Babcock's Translation of Pellagra, by Dr. A. Marie, on page 144, there occurs the following statement, probably founded on Lombroso's writings: "The statements are somewhat discordant, but most authors agree that the disease does not occur in infants unless they are fed on spoiled corn." There are numerous other distinguished authorities who have denied the existence of the disease in infants, but time and space will not permit mention of their names. It has been abundantly proved, however, that numerous cases do occur among infants, and we know now that there are many cases in which the infant's food consists entirely of its mother's milk.

I have carefully examined the leading works on diseases of children published in the United States and in England, and in none of them have I found any mention of pellagra. Simonini, in 1905, says that no book on diseases of children contains a chapter on pellagra. This statement is meant to apply to Italy, where, of course, we are aware there are hundreds of cases of pellagra in infants. From the importance of the disease, the omission should be corrected.

Pellagra, from the pediatric point of view, is a subject of most absorbing interest. Until two years ago I do not recall having seen the disease in early childhood, but as soon as I commenced giving the question attention and looking for the disease, the cases were found, and they seem to increase more rapidly as time goes on. Among the more important practical questions that pediatrists have to answer is, whether the baby shall be allowed to nurse a pellagrous mother. After careful examination of the scant literature on the subject, and from the experience of those whom I have consulted, as well as my own, I am forced to answer in the negative. Babies who nurse pellagrous mothers invariably suffer from intestinal disorders, become marasmic and show marked symptoms of rickets. Whether the cause is due to a food deficient in quantity, as well as quality, is still a question of some doubt. However, Agostini found, after examining the milk of many pellagrous mothers, that while the milk showed a composition not very different from the normal in fats and sugars, it also showed a deficiency in casein and an excess in salts. Simonini confirms these observations. Lucatello has demonstrated a marked diminution of iron in the blood, and Simonini a marked deficiency of iron in the milk, of pellagrins. Bonservizi says that children born of pellagrous mothers are the surest candidates for the disease. Simonini and many other writers have expressed like opinions. Nearly all the Italian pellagrologists who mention children call attention to the fact that infants born of pellagrous mothers are under weight and that a large percentage of them die before reaching the fifteenth month; among the more common causes of death are gastro-enteritis, bronchitis, bronchopneumonia and eclampsia. Despite this apparently unfavorable outlook, there are authorities who state that if the baby is early changed to the breast of a strong, healthy wet-nurse and removed from the endemic area, the child will not only escape the disease but will grow and develop normally.

### FREQUENCY OF PELLAGRA IN EARLY CHILDHOOD

Practically no statistics are available in the United States by which the relative frequency of pellagra in children can be even approximately calculated.

I communicated with about one hundred physicians who I was sure would probably recognize the disease if they saw it. With few exceptions the men communicated with lived in the smaller towns in which industrial plants were situated and pellagra existed. Some of these men have not responded to my repeated appeals. In some instances my correspondents replied that they understood that pellagra did not occur in young children, but since being informed that it did, they would look for it. In three or four cases it was later found. Seventy-seven physicians reported cases under 4 years of age. In a number of their answers the observers reported having seen two or more cases.

So far as I have been able to ascertain, there have been probably fifteen cases in children under 4 years of age, occurring in the township in which Columbia is situated, containing about 65,000 people. The youngest case from this community was 5½ months old. The youngest case which I have seen reported is two months old. There are a great many cases reported between 4 and 10 years of age. One orphanage reported fifty-seven cases of pellagra out of a total population of 215, the average age being 10, the youngest 5 years. In a small area of which I have personal knowledge, eleven cases have occurred, ranging in age from 15 months to 6 years.

Cases in infants are being observed so much oftener now than they were even a year ago that we are led to the conclusion that pellagra in infants is by no means a rare occurrence. It will be well for us to bear in mind the experience of the Italian and Roumanian physicians, where at one time pellagra in infants was denied but now is frequently recognized. The history of pellagra teaches, among many important facts, that because of its varied and varying manifestations, it is most easily overlooked and the case branded with a mistaken diagnosis. And while this is commonly admitted as applying to adults, it applies with especial force to younger children and infants.

## ETIOLOGY OF PELLAGRA

*Age.*—No age is exempt. We have reliable histories, by Sambon and others, of cases ranging in age from a few weeks to 104 years. The disease, however, has not been often observed in infants under 3 or 4 months. It is fairly frequent between 6 and 18 months, and quite common beyond 2 years of age.

*Sex.*—In children the disease seems about equally distributed between the sexes. (Simonini; Agostini.)

*Climate.*—No climate or country seems exempt.

*Season.*—Most of the attacks occur in the spring, early summer, or autumn. It is unusual for cases to appear during cold weather.

*Heat.*—The rays of the sun seem to aggravate the rash and act as an exciting cause. It must be remembered, however, that protection from the sun's rays does not always prevent the rash.

*Surroundings.*—Pellagra is usually found amidst insanitary surroundings, whether in the rural districts, mill villages or cities.

The cause of pellagra is by no means settled. Time does not permit even a brief review of many of the etiological hypotheses. So far I shall merely mention the leading ones.

Pellagra has been described under many names. Among the most prominent are mal de la rosa, mal del sole, mal de misère, maidismus, Alpine scurvy, Asturian leprosy, Asturian rose, psychoneurosis maidica, disease of the Landes, Lombardy erysipelas, etc. Practically since anything was known or written of the disease its cause has in some way been associated with the eating of Indian corn.

Gaspar Casal of Spain, in 1735, was probably the first to describe the disease. He uses the name mal de la rosa, a term that he affirms had long been in common use among the Spanish peasants. He ascribes the causes to atmospheric conditions and to eating maize. His work was not published till 1762.

Frapolli of Italy, in 1771, in describing the disease, first used the term in general use among the Italian peasants—pellagra, which he spelled with one "l," meaning rough skin. He attributes the cause to insolation. In 1776, the Venetian Board of Health attributed the disease to spoiled corn. Following this, and covering a period of approximately seventy-five years, there was little progress made towards solving the etiology of the disease, and few hypotheses were seriously advanced at variance with the maize theory (and none successfully withstood the storm of criticism that was aroused), until 1848, when Ballardini denied that the eating of sound corn was injurious, but affirmed that pellagra was caused by eating corn that had become spoiled from a mould, the *Sporosum maidis.* Ballardini was undoubtedly the founder of the spoiled corn theory of pellagra, and it was his work that probably stimulated Lombroso, in 1864, to undertake his exhaustive study and experiments on maize and its relationship to pellagra. His work extended over a period of twenty-five years, and has been of so impressive a nature that his views are probably held by the great majority of Italian physicians and by many elsewhere, notably Merk, Babes, Zion and many other distinguished pellagrologists. Lombroso's theory is that pellagra is an intoxication produced by the action of certain organisms on corn. These organisms are harmless unless in contact with the kernel of the grain, where they produce a ptomain.

Efforts have been made at various times to recover the bacillus maidis in the blood of pellagrins, but so far they have not been successful.

The work of Ceni, because of the eminence of the man and the thorough character of his work, entitles his hypothesis to consideration. He observed that people who had never eaten the products of corn, but had eaten the products of other cereals, had pellagra. He made numerous experiments and found that the same micro-organisms which develop on spoiled corn can grow on other cereals, with the same characteristics and the same toxic power. He says: "Pellagra is not and cannot be anything but a toxicoparasitic morbic process due to vegetable micro-organisms, endowed with various and opposite specific toxic properties which correspond to the varied symptomatology of this affection."

Simonini says: "It is now proven that the spores of *Aspergillus fumigatus* only can penetrate the intestinal wall and invade the system." It is interesting to add that the biological cycle of the *Aspergillus fumigatus* develops in the beginning of spring and of summer, the *Aspergillus flavescins* in autumn. Their toxic activity is greatest at the seasons mentioned.

Men of note have advanced the theory that pellagra is due to a food deficiency, like beriberi, scurvy or rickets, and that the remedy when found will be like Dr. Casimir Funk's "vitamine."

In 1905 Prof. Louis W. Sambon of London announced that he believed that pellagra might be an insect-borne parasitic disease and that the specific parasite was probably a protozoal organism. Since then Professor Sambon has carried on extensive and careful investigations in various parts of Europe, and recently in America. In a recent address he definitely and emphatically denies that maize, either good or bad, has anything to do with the cause of pellagra. He noted the following objections to the maize theory:

1. There is no foundation whatever for the belief that pellagra broke out in Europe soon after the introduction of maize from America.

2. The topographical distribution of pellagra does not coincide either with the distribution of maize cultivation or with maize consumption.

3. The disease occurs frequently in persons who have seldom or never partaken of maize as an article of food.

4. All preventive measures based on the maize theory have failed.

5. The characteristic skin eruption and other symptoms of the disease may recur each spring for several successive years in patients who are far removed from the endemic districts and who abstain from maize.

In the place of the maize theory Professor Sambon advances the simulium theory, and gives the following reasons:

1. Pellagra is a parasitic disease, because:

(*a*) The characteristic eruption and other symptoms of the disease may recur each spring for a number of years, notwithstanding the removal of the patient from the endemic districts and the strict elimination of maize from his diet. This peculiar periodicity of symptoms can be explained only by the agency of a parasitic organism presenting definite alternating periods of latency and activity. Analogous periodicities are met with as in the other parasitic diseases, as, for example, in tertian fever, in which the periods of activity of the parasite (*Plasmodium vivax*) recur each summer in correlation with the activity period of its anophelic definitive host; no toxic substance could account for it.

(*b*) It presents peculiarities of distribution and seasonal incidence as in all parasitic diseases.

(*c*) Its symptoms, course, duration, morbid lesions are analogous to those of other parasitic diseases.

2. It is an insect-borne disease, because:

(*a*) It is not directly contagious.

(*b*) Neither food nor drinking water can account for its peculiar epidemiology.

(*c*) It is limited to certain rural districts only, towns and villages almost invariably escaping.

(*d*) It presents a definite and peculiar seasonal incidence, viz., spring and autumn.

(*e*) It is practically restricted to only one class of people, viz., the field laborer, owing to the greater exposure to infection.

3. It is conveyed by a simulium, because:

(*a*) Simulium, so far as we know, appears to affect the same typographical conditions as pellagra.

(*b*) In its imago stage it seems to present the same seasonal incidence.

(*c*) It is found only in rural districts, and, as a rule, does not enter towns, villages or houses.

(*d*) It explains most admirably the peculiar limitation of the disease to agricultural laborers, a limitation which nothing else can explain in a satisfactory manner.

(*e*) It has a wide geographical distribution which seems to cover that of pellagra, although certainly exceeding it in the same way that the distributional area of the anophelinae exceeds that of malaria, and the range of *Stegomyia calopus* that of yellow fever.

(*f*) It is known to have caused several epizootics in Europe and America.

(*g*) Other similar blood-sucking diptera such as *Phlebotamus papatassi* and *Diplophus febrilis* are strongly suspected of being propagators of human diseases.

The work of Sambon has certainly stimulated a new line of investigation which is being carried on by many able scientists with zeal and enthusiasm. Through its influence many have discarded the maize theory, and many others who have never held it have been strengthened in their opinion. This, however, does not mean that they accept the simulium theory, because there are many who believe the disease is a protozoan disease but do not believe that the simulium is the carrier. Jennings and King,[1] members of the Thompson-McFadden Pellagra Commission, incline to the *Stomoxys calcitrans* as the carrier of the disease. They say:

> The buffalo gnats (Simulia) should be eliminated, principally by the facts of their biting habits and lack of those of intimate association with man; also by their comparatively moderate abundance (in our territory). We find that in Spartanburg County they are hardly known as a pest of man, and when they do attack him it is very locally and largely confined to field workers. Had Sambon's theory not been advanced, these flies could hardly have attracted suspicion in any connection with pellagra in this country.

Still others (Roberts) incriminate certain mosquitoes.

## SYMPTOMS AND CASES

Some authors, notably Sandwith and Merk, speak of a more or less well-defined incubation period. The shortest period, eleven months, mentioned by either of the two named, is evidently a mistake, since the disease occurs in early infancy in cases in which heredity could not possibly play any part. I think it is safe to assert that no definite incubation period has been determined.

One of the facts about pellagra on which there exists no difference of opinion is that it presents many protean types. Despite the truth of this observation, a very clear picture of the disease can usually be worked out. Most of the cases present definite gastro-enteric disturbances, certain nervous manifestations and symmetrical skin lesions. This last symptom is considered pathognomonic. The disease may come on in a child that has seemed previously in good health, properly nourished and well developed. The course may be so insidious that the first symptom to arouse suspicion is the rash. Even then the child may not appear sick, and if it is old enough to have been exposed to the sunlight, nothing is thought to be unusual or of sufficient importance to consult a physician, unless there are several other cases in the immediate

1. Jennings and Kling: Am. Jour. Med. Sci., Sept. 1913, p. 439.

neighborhood, or cases of a similar nature in the immediate family. The following case, referred to me by Dr. J. W. Babcock, well illustrates this condition:

CASE 1.—T. M. C., white, male, aged 4½ years, lives in a cotton-mill village near the central portion of South Carolina (Fig. 1). Family history is negative, except paternal grandfather was a chronic alcoholic. Father in good health. Mother was well until three weeks ago, when she developed a diarrhea and rash on hands and feet.

The child was a full term, normal baby; weight at birth not known; breast fed and perfectly well until 2 years of age, when the child had ileocolitis

Fig. 1.—T. M. C., white, aged 4½ years; first attack of pellagra; convalescent.

which lasted about two weeks, from which convalescence was rapid. The child is well developed and well nourished. Heart and lungs normal. Abdomen appears normal in size. There is no tenderness elicited by deep palpation anywhere over abdomen. Rash on forehead, neck, dorsal surfaces of hands, wrists, feet and ankles, now fading, appears gray and scaly around the edges, but much whiter towards the center than is the skin elsewhere on the body. Rash appeared four weeks previously; three weeks after appearance of rash diarrhea commenced, but was never severe and lasted only a few days. The tongue is red and fissured, and fissures are present in the angles of the mouth. The child has an anxious expression and seems dejected. Knee-jerks exaggerated.

The father of this child says that it has seemed well, except for the burning and itching over the areas of the rash and the slight diarrhea. Thirst has been marked since the rash commenced. He gives a history of two cases, in children aged 5 and 9, within fifty feet of his house.

It is not infrequent to find that a serious diarrhea is the symptom that causes anxiety in the parents, the rash appearing subsequent to the diarrhea. Case 2 illustrates this type of the disease.

CASE 2.—A. M., white, American, female, aged 3, was brought to the Richland Dispensary because of diarrhea which had lasted for three weeks. This condition started by the child having two or three loose, watery stools a

Fig. 2.—Annie V., white, aged 6; fifth attack of pellagra; first attack occurred before the age of 2.

day, which had gradually increased until she had from twelve to fifteen a day. The grandmother, who brought the child, says that until the diarrhea commenced the child was the picture of health. She attributed the diarrhea to some turnips which she thought the child had been given by her little cousin. About one week ago there appeared a slight reddening of the dorsal surface of the hands and wrists and feet and ankles. The patient was given castor oil and paregoric for the diarrhea, but the effect was only temporary. She said that the child had no appetite, but drank a great quantity of water. It complained of sore mouth and a burning sensation of the tongue, but she paid little

Fig. 3.—Josiah P., aged 18 months; wet variety of pellagra. (By courtesy of Dr. J. J. Watson, Columbia, S. C.)

attention to this as she had often observed that children had that condition as a result of indigestion, which she thought was also caused by the turnips.

Three of the grandparents of this child are alive and well; the other, the paternal grandfather, died of pneumonia. Her father is alive and well. Her mother, of previously good health, died about one year ago of typhoid fever. The child is well developed, but is emaciated and very anemic. Temperature, 97.6 F. She appears quite sick. The tongue is red and is covered with a

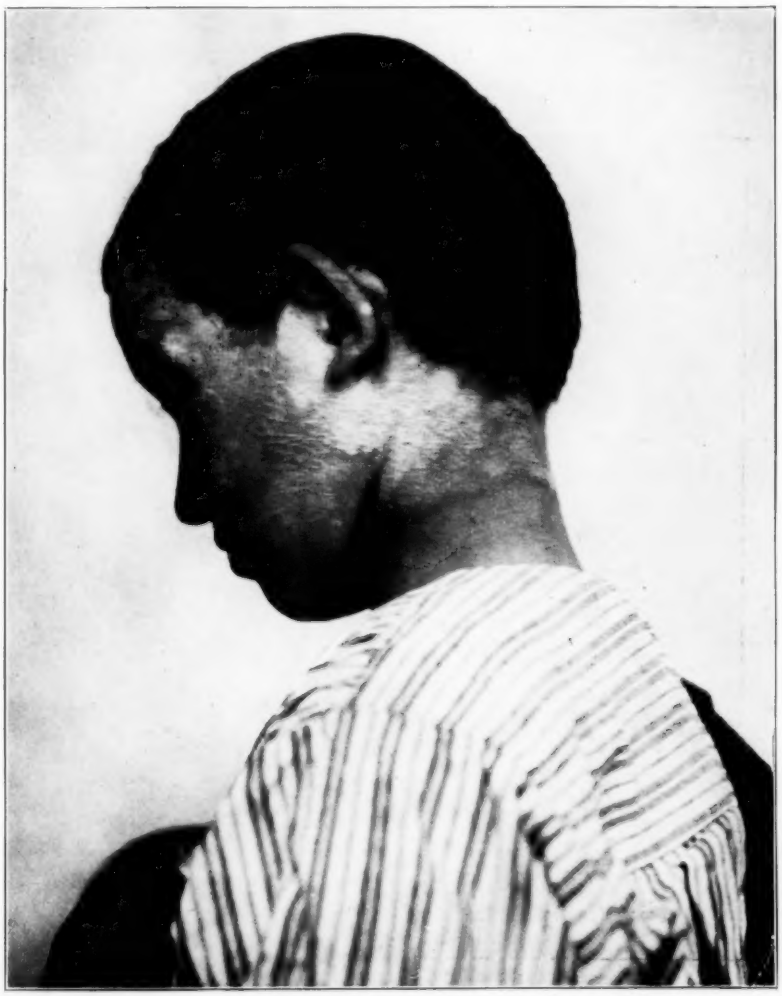

Fig. 4.—Pellagra in Italy. Photograph from Dr. Eugenio Bravetta, Mombello, italy.

tenacious mucus; the gums are also red and swollen, suggesting scurvy. The organs of the thorax are normal. The abdomen is distended, soreness being manifest on deep palpation. No rash about face or neck, but a definite symmetrical erythema on the dorsal surface of the hands, wrists, feet and ankles. The erythema on the hands and wrists was rather pinkish than red, and

the skin was dry and rather thickened and hard, while the rash on the feet and ankles was gray colored, scaly and very rough. The hands and wrists were slightly swollen, and the patient constantly scratched them. There was no swelling about the ankles and feet. Knee-jerks appeared normal, ankle clonus absent.

Constipation may be present instead of diarrhea, or constipation may persist for some time, followed by diarrhea. The rash may be present for only a short time, then disappear, the other manifestations of the disease remaining. The following case illustrates what appears to be pellagra-sine-pellagra.

Fig. 5.—Pellagra in Italy. Photograph from Dr. Eugenio Bravetta, Mombello, Italy.

CASE 3.—Robert W., Jr., a mulatto, aged 5½ months. Full term; normal delivery; entirely breast fed. Was not weighed at birth. The baby is well developed, but only fairly well nourished. The mother says the child was in splendid health until 4½ months old, when constipation became so troublesome that a physician was called; the child cried a good deal from pain, would draw up its legs, and become so nervous that she feared convulsions. When I

saw the child, about two weeks afterward, I observed that the tongue was red around the edges and on the tip; had slight fever, never going above 101 F. The patient appeared very sick at this time; diarrhea had set in and he was having ten to fifteen foul-smelling, watery stools a day. The infant was taken from the breast and put on boiled water. No improvement followed. Rice water was then tried, but with no effect. This was followed by casein milk (Eweissmilch). He seemed to improve slightly, but the bowels were still quite loose. I made repeated examinations, but could find nothing that would suggest anything more than severe diarrhea. Insomnia was most persistent, despite the usual remedies, and now the child moaned almost constantly. Finally, on the twelfth day of my attendance, I observed a rash on both feet and ankles, and a slight discoloration on the dorsal surface of the hands which gradually faded out at the wrists. The rash on the feet was absolutely symmetrical, as was the discoloration on the hands. The day following, much to my surprise, the rash had disappeared, and where it had been the skin was smooth and glistening and somewhat swollen, the vessels were very much dilated and stood out very prominently. Three days later this child died.

This case is very interesting and instructive, because both parents were strong and healthy. There was no history of pellagra in any other member of the family, and the child was entirely breast fed. The rash disappearing so quickly and leaving the purpuric condition was most unusual. Babcock had never seen it before, and Simonini mentions having seen but one case.

The rash in pellagra assumes both the dry and wet forms. Just why the eruption in one case should be dry and in another, in the same locality, it should be bullous, has not been satisfactorily explained. The rash may spread over the entire face, as may be seen in one of the photographs presented. A short time ago I saw a case in which the rash was perfectly symmetrical on the hands and feet, but was present over the abdomen as well. It sometimes occurs on the ulnar surface of the forearm and extends to the elbow. In children it occurs occasionally in the palms of the hands and on the soles of the feet. I have seen it in children extend up the front of the legs to the knees. Dr. W. A. Boyd has in his practice three little brothers that illustrate beautifully this distribution of the rash.

Where there have been several exacerbations of the rash the skin becomes much thickened and is hard. Not infrequently it shows a definite tendency to fissure. Light appears to aggravate the intensity of the erythema, but it cannot be said to ever cause it, because, while it appears on the exposed surfaces, protection from light by gloves, etc., does not prevent it.

## SYMPTOMS AND SIGNS

*Digestive Symptoms.*—While it is difficult to lay down a hard and fast rule, it is generally conceded that in very young children the digestive disturbances are very much more pronounced than in children after the fourth year. Not only do young children suffer from

indigestion, but also from severe diarrhea. The diarrhea may consist of frequent large, watery stools, or frequent stools containing mucus and blood, or constipation may exist.

*Nervous Symptoms.* — Paresthesia is usual. The knee-jerks are generally exaggerated. Insomnia is marked. Depression occurs in many of the cases. In older children it is almost the universal observation that the symptoms run a milder course than either in very young children or in adults.

*Blood.*—There is nothing found especially characteristic in the blood of pellagrous children. A slight increase in the mononuclears has been observed.

### DIAGNOSIS

In most cases of pellagra in young children, if we are to meet with success in treatment, its prompt recognition is essential. The numerous blood serum tests that have at various times promised hope have proved to be unreliable, and the indican test, while positive in many cases, cannot be depended on. Whether or not one may be justified in making the diagnosis of pellagra in children without the presence of the rash, may still be considered an open question. Certainly, in a territory in which the disease is unknown or unrecognized, that is occurring in sporadic cases, such a diagnosis may be open to criticism. Still, I am not prepared to say that such a diagnosis cannot or should not be attempted. Given a child with a red tongue, fissured lips and diarrhea, together with such nervous symptoms as headache, insomnia, restlessness, paresthesia and brisk or absent knee-jerks, or the more advanced symptoms of spasms, rigidity and photophobia, the diagnosis of pellagra should be considered. Simonini lays great stress on muscular weakness in the lower extremities as an important early symptom of the disease. Not infrequently while the final diagnosis based on such a group of symptoms as above described is still being held in abeyance, the development of an erythema, however slight or transient, on the dorsi of the hands or feet, on the knuckles, elbows or wrists, or at the angle of the thumb and index finger, as well as over the patellae, serves to confirm a tentative diagnosis of pellagra.

Of course, in a region where pellagra is endemic, this kind of diagnosis is much less hazardous. One of my purposes, however, in preparing this paper, is to put pediatrists on notice that the time has arrived, at least in the United States, when they must, in doubtful cases presenting such a symptom-complex, consider pellagra a possibility and not wait for all the classical manifestations of the malady to be present before either making the diagnosis of pellagra or suspecting its possibility. Cases of undoubted pellagra have been under observation in some of our best hospitals without finally being diagnosed, because they had not presented all the symptoms laid down in the books.

If, however, the erythema be present, without one or the other of the triad of symptoms, the diagnosis ought to be made. When the case presents the association of intestinal, nervous and skin manifestations—the classical triad—then the diagnosis of pellagra is inevitable.

### PROGNOSIS

The opinion seems to prevail that in pellagra the younger the infant when the disease fully develops, the less favorable is the prognosis. Certainly, infants at the breasts of pellagrous mothers sink rapidly into marasmus unless given a change of diet. Children from 4 to 10 years of age seem liable to a milder type of the disease, and when given the benefit of generous dietary and change of environment, they usually recover. They should, however, be kept under observation for several years, since the problem of recrudescence in pellagra seems still to be one of uncertainty as regards permanent prophylaxis, and the measures contributing to it.

### TREATMENT

It has already been made sufficiently clear in this paper that nurslings, either with or without the suspicion of having pellagra, should usually be weaned from pellagrous mothers. Not only should a change of diet be ordered for such infants, but in view of our uncertainty as to the real cause of the malady, a change of environment should be ordered, or if this is not possible, patients should be placed in the best hygienic surroundings.

Among hygienic measures for the treatment of pellagra, after careful nutrition, hydrotherapy has ranked high from the time of Frapolli. The influence of sunshine in developing the erythema points to its avoidance as a preventive measure. Local measures, such as calamine lotions, are of advantage in alleviating the acute dermatosis. Internally, tonics such as arsenic and iron are of benefit. The frequent association of intestinal parasites should be kept in mind and, when discovered, eliminated. Other associated conditions—cretinism, malaria, tuberculosis and syphilis—should always be sought for, since pellagra seems often to select weaklings.

In conclusion, I wish to express my gratitude and return my thanks to Dr. J. W. Babcock for placing at my disposal his generous library on pellagra, and for assistance in many ways in the preparation of this paper; also to the many physicians who have reported cases to me.

I regret that space does not permit me to refer to the bibliography which has been at my disposal in the preparation of this paper, but any one who desires to look the matter up will find the library of the Surgeon General's office fairly complete. I especially wish to refer to Simonini's monograph on "Pellagra in Infants and Children" as being most excellent.

# SPASMOPHILIA WITH ESPECIAL REFERENCE TO FAMILIAL REACTIONS AND REPEATED ABSENCES *

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MINNEAPOLIS

New light has been thrown on the subject of convulsions and allied conditions in childhood by the study of the electrical reactions. This work was begun and carried out for years by Escherich.[1] General convulsions in children, laryngospasm, spasmodic apnea, tetany and similar phenomena have been shown to be but manifestations of an underlying hyperexcitability of the peripheral nervous system, with a tendency to tonic and clonic spasms, the so-called spasmophilic diathesis.

Mechanically the hyperirritability can be shown by tapping over the seventh nerve along its course in the cheek, with a resulting contraction of the muscles around the mouth. Tapping over the upper branches of the same nerve may produce a similar contraction about the eye. The first is known as Chvostek's and the second as Weiss' phenomenon. Constriction of the arm in this condition at times brings on the tetany position of the hand—Trousseau's phenomenon. The Chvostek and Weiss phenomena are therefore indicative of spasmophilia. The Trosseau phenomenon is pathognomonic.

More important, however, because they can be more accurately measured, are the electric reactions. In the normal child, with the Stinzing electrode applied over the peroneal nerve, no cathodal or anodal opening contraction is produced with less than five milliamperes of galvanic current. Charts 1 to 6, as given by von Pirquet,[2] show the normal reactions as well as those of hyperexcitabiliy.

The first column, C C C, represents cathodal closing contraction, the others in order, A C C, anodal closing contraction, A O C, anodal opening contraction and the fourth, C O C, cathodal opening contraction. The amount of current necessary to produce the contractions is shown by the height of the blocking indicated by the number of milliamperes on the left of the standard specimen blank chart above charts 1 to 6.

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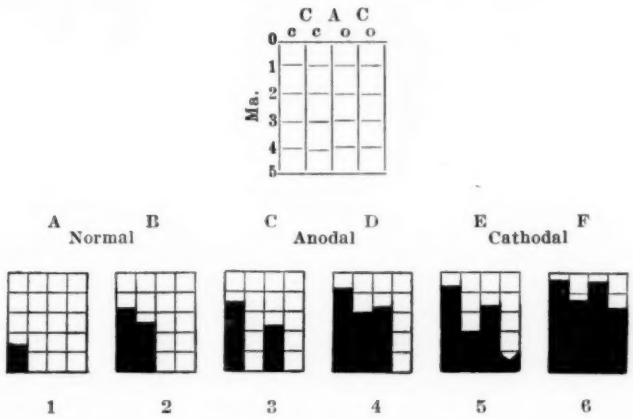
* Read in the Section on Diseases of Children of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

1. Escherich, Theodor: Die Tetanie, Hölder, Vienna and Leipsic, 1909
2. Cited from Escherich: Die Tetanie.

The study of the electrical reactions has shown that there may be a latent spasmophilic condition or an active state with such manifestations as have been mentioned above. Ibrahim states that at certain times of the year 30 per cent. or more of the children show spasmophilia latent or active. The importance of the recognition of this latent condition, in order that the proper prophylactic treatment for the prevention of convulsions may be instituted, is evident.

Characteristic pathologic anatomic changes have not been shown in the nervous system of spasmophilics. Escherich, basing his conclusions on the work of Yanase and Erdheim, considered the condition due to changes in the parathyroids. Later, negative findings by various investigators have, however, thrown doubt on this hypothesis.

The studies of Quest and others on the brains of infants indicate a low calcium content in these cases. Mac Callum and others have demon-




Charts 1-2.—Normal reactions given by von Pirquet.
Charts 3-6.—Hyperexcitability reactions given by von Pirquet.

strated that the calcium of the brains of animals suffering with tetany parathyreopriva is low. Cohn and Cooke have on the other hand, had somewhat contradictory results. Herman Schwarz[3] suggests that these conflicting results may mean that it is the calcium-sodium ratio which is of most importance, as in the case of this character in which the calcium content was high the sodium content was also high, making in one of Aschenheim's cases a quotient of forty-six instead of the normal one from nineteen to twenty-six. Although Gerstenberger did not succeed in obtaining improvement in these cases by the oral administration of calcium lactate and Grulee's metabolism work gives little or no con-

3. Schwarz, Herman, and Bass, Murray H.: The Calcium Metabolism in Infantile Tetany, with Report of a Case, Am. Jour. Dis. Child., January, 1912, p. 15.

firmation of this hypothesis, it is very probable that there is some relationship between spasmophilia and the calcium metabolism.

Manifestations of spasmophilia are much more common in the late winter and early spring months. Breast-fed children are rarely affected. According to Finkelstein[4] the whey of cow's milk is an exciting factor. Infectious diseases or alimentary disturbances may change a latent spasmophilia into an active condition with convulsions. Rickets and spasmophilia frequently occur together.

It has long been recognized that this condition is hereditary or familial. The literature, however, shows few records of familial electric reactions. Schiffer[5] reports one family in which the mother and one child of 15 years gave normal electric reactions, and two of the children showed hyperelectric excitability.

Toyofuku[6] took the electric reactions of four newly born puppies whose mother had been subjected to the removal of the thyroid and parathyroid glands. All four showed marked tetany reactions. The mother showed definite signs of tetany and heightened electric reactions after the birth of the puppies. He considers the condition as a lactation tetany. He believes that a tetany or tendency to tetany may be transmitted through the milk. Without knowledge of this work on dogs I have examined the electric reactions of the mothers of the somewhat rare cases of spasmophilia in breast-fed children which have come to my attention, and have found the irritability of the mothers almost uniformly high.

CASE 1.—John D. was 5½ months old when first seen by me, March, 1911. He was still at the breast. His aunt had had convulsions as a child and she is now mentally deficient. The mother stated that she took four quarts of milk and cream daily during her pregnancy and at the time of the examination her diet was almost wholly made up of milk and cream. The infant was brought to me because it had had repeated convulsions. The child was markedly rachitic with pronounced craniotabes. His electrical reactions were spasmophilic as shown in Chart 7 (April 13) and Chart 8 (July 18).

7 8 9 10 11 12

Charts 7 and 8.—John D., Case 1, April 13 and April 18, 1911.
Chart 9.—The nursing mother of John D., Case 1, July 25, 1911.
Charts 10 and 11.—Anne B., Case 2, Nov. 22 and Nov. 26, 1912.
Chart 12.—The nursing mother of Anne B., Case 2, Nov. 22, 1912.

4. Finkelstein: Lehrbuch der Säuglingskrankheiten, Berlin, 1905, Part 1, p. 248.

5. Schiffer: Ueber familiare chronische Tetanie, Jahrb. f. Kinderh., 1911, lxxiii, 601.

6. Toyofuku, T.: Beitrag zum experimentellen Studium der Lactationstetanie, Jikazasshi M. 130, 1911; Cited from Ztschr. f. Kinderh., 1911, i. R., p. 592.

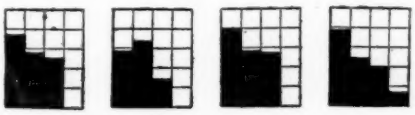
The markedly spasmophilic reactions of the nursing mother of John D. are given in Chart 9 (July 25).

CASE 2.—Anne B. was 5 months old and at the breast at the time of her first examination. She had rickets with marked craniotabes and gave the reaction shown in Chart 10 (November 22) and Chart 11 (November 26).

The nursing mother gave a marked Chvostek phenomenon and her electrical reactions were striking, as shown in Chart 12 (November 22).

CASE 3.—William R. was 9 months old and at the breast when he came under my care, Nov. 14, 1912. He had had repeated convulsions from his fourth month. He still has convulsions and there is a decided mental injury. His reactions are shown in Chart 13 (November 15) and Chart 14 (December 15).

The nursing mother's reactions show marked hyperexcitability, Chart 15 (November 15), and Chart 16 (November 20).



13 14 15 16

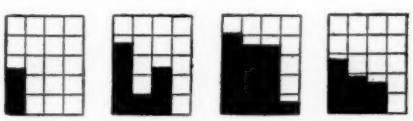
Charts 13 and 14.—William R., Case 3, Nov. 15 and Dec. 15, 1912.
Charts 15 and 16.—The nursing mother of William R., Case 3, Nov. 15 and Nov. 20, 1912.

CASE 4.—E. G., a girl of 3 months, and at the breast, had convulsions, but no demonstrable hyperelectrical excitability, Chart 17 (September 4). She had been given chloral hydrate.

The nursing mother, however, gave evidence of hyperexcitability on the same day. Chart 18 (September 4).

CASE 5.—George L. died at the age of 1 year with broncho-pneumonia and beginning tuberculous meningitis following pertussis. There was marked tetany for some time before death. Unfortunately, the child's reactions could not be taken, but the reactions of the mother, who was nursing him, are shown in Chart 19 (May 29).

CASE 6.—Irma E. was under my care at the age of 6 months with pyelocystitis. Although her electrical reactions were not taken, she had marked tetany of both hands. The nursing mother's reactions are given in Chart 20 (October 29).



17 18 19 20

Chart 17.—E. G., Case 4, Sept. 4, 1912. Chart 18.—The nursing mother of E. G., Case 4, Sept. 4, 1912.
Chart 19.—The nursing mother of George L., Case 5, May 29, 1912.
Chart 20.—The nursing mother of Irma E., Case 6, October 29, 1912.

In but two cases of spasmophilia which I have seen in infants at the breast, the mothers have not shown very marked electric excitability. One of these children showed marked carpopedal spasm, but was getting

other food as it was in its third year. The other was also older, 2 years and 3 months, and also had marked tetany.

To recapitulate: In all of the cases of infants, 1 year or less of age at the breast whom I have examined and found spasmophilic, the nursing mothers have shown definitely heightened electric excitability.

The electric reactions of other members of the families of spasmophiliacs often bear out the frequently made assertion that the condition is hereditary or familial.

CASE 7.—In the family of Baby J. D., as shown by Chart 21 (August 1), the mother, brother and aunt have heightened electric reactions, as well as Chvostek phenomena, Chart 22 (July 25), Chart 23 (November 21) and Chart 24 (October 22). The aunt had had convulsions as a child and is now mentally deficient. An uncle had had convulsions during his first year. The grandmother presented a marked Chvostek phenomenon, but without heightened electrical excitability (Chart 25).

21 22 23 24 25

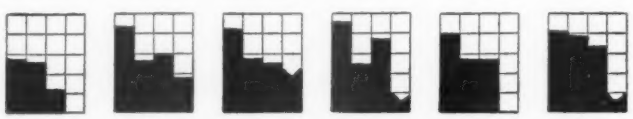
Chart 21.—John D., Case 7, Aug. 1, 1911. Chart 22.—The mother of John D., Case 7, July 25, 1911. Chart 23.—The brother of John D., Case 7, Nov. 21, 1912. Chart 24.—The aunt of John D., Case 7, Oct. 22, 1912. Chart 25.—The grandmother of John D., Case 7.

CASE 8.—Baby R. R., with convulsions and a marked Chvostek phenomenon, gave spasmophilic reactions. (Chart 26, February 13). The mother's reactions are shown in Chart 27 (December 26).

CASE 9.—Baby Q. T. had convulsions and marked spasmophilic reactions. (Chart 28, December 28).

The mother had had convulsions as a child and the high reactions shown in Chart 29 (December 28).

CASE 10.—Theo. McC. has had convulsions, and his mother gave similar reactions. (Charts 30 and 31, March 21.)



26 27 28 29 30 31

Chart 26.—Baby R. R., Case 8, Feb. 13, 1913. Chart 27.—The mother of Baby R. R., Case 8, Dec. 26, 1912.

Chart 28.—Baby Q. T., Case 9, Dec. 28, 1912. Chart 29.—The mother of Baby Q. T., Case 9, Dec. 28, 1912.

Chart 30.—Theo. McC., Case 10, March 21, 1913. Chart 31.—The mother of Theo. McC., Case 10, March 21, 1913.

CASE 11.—Baby B. J. gave spasmophilic reactions (Chart 32, July 27), the mother did not, but the father did (Charts 33 and 34). All three showed the Chvostek phenomenon, the father's being especially marked.

CASE 12.—This is also true of Virginia J. (Chart 35, April 3), her mother (Chart 36, March 1), and father (Chart 37, November 1).

32 33 34 35 36 37

Chart 32.—Baby B. J., Case 11, July 27, 1912. Chart 33.—Mrs. J., the mother, Case 11. Chart 34.—Mr. J., the father, Case 11.
Chart 35.—Virginia J., Case 12, April 3, 1913. Chart 36.—The mother of Virginia J., Case 12, March 1, 1913. Chart 37.—The father of Virginia J., Case 12, Nov. 1, 1912.

CASE 3.—Baby W. R., had active spasmophilia for months with reactions shown in Chart 38 (November 20).

Mrs. R., his mother showed marked hyperexcitability (Chart 39, November 20). His father (Chart 40, November 21), as well as his parents, the grandmother and grandfather (Charts 41 and 42, November 20), showed less marked evidences of hyperexcitability.

38 39 40 41 42

Chart 38.—William R., Case 3, Nov. 20, 1912. Chart 39.—The mother of William R., Case 3, Nov. 20, 1912. Chart 40.—The father of William R., Case 3, Nov. 21, 1912. Chart 41.—The paternal grandmother of William R., Case 3, Nov. 20, 1912. Chart 42.—The paternal grandfather, Case 3, Nov. 20, 1912.

CASE 13.—The B. family, in which the father had had convulsions as a child, consisted of nine children, eight of whom had had convulsions in childhood. The three who could be examined gave the heightened reactions shown in Charts 43-45, together with the Chvostek phenomenon. The last reaction is interesting as it is that of the only son who did not have convulsions, showing a latent spasmophilia.

43 44 45 46 47

Chart 43.—Mr. B., Case 13. Chart 44.—The son of Mr. B., Case 13. Chart 45.—The only son of Mr. B. who did not have convulsions.
Charts 46 and 47.—S. S., Case 14, Aug. 3 and Sept. 12, 1912.

Further repetition from my records would only consume time. The cases in which one or both parents of spasmophilic children do not give like reactions are exceptional.

We are indebted to Friedmann for the recognition of the character of the repeated non-epileptic "absences" in children, which so resemble

petit mal. He considers that they bear no relation to epilepsy and apparently have nothing to do with hysteria. They are characterized by the following peculiarities: They begin in apparently well children from the fourth to the seventh year, usually suddenly after some excitement, such as fear or operation. They consist of short, light disturbances of consciousness without convulsions and without falling. They come on at first in a great number of attacks (6 to 10 to 100 a day and occasionally at night). The course of the disease is tedious, usually being from seven to eight years. There may be also long remissions. They have no disturbing influence on the mental or bodily development of the child. This is a chief argument against their relation to epilepsy from which they, moreover, differ, in that the occurrence of convulsive attacks is almost never observed (*fast völlige Ausbleiben*). They are also to be distinguished from epilepsy by the history. Against their hysteric nature, the uniformity of the attacks, in spite of continuance for years as well as the lack of other symptoms which would make one suspicious of hysteria, may be cited. The "repeated absences" present a good prognosis in that they appear to clear up before puberty even without treatment. So far as the systematic placing is concerned, they may be related to the narcolepsy of Gelineaus and the other somewhat half-understood "neurotic absences" of adults. It seems that they appear on the foundation of a spasmophilic diathesis as, in the three cases which have been so far recently tested electrically, the increase of electric excitability and cathodal opening contraction with less than 5 milliamperes has been observed (two of these observations were made by Mann).

CASE 14.—S. S., aged 7, seen first Aug. 3, 1912. She has been under my observation during the past year and illustrates the above condition as described by Friedmann. Her father and mother are living and well. She was a full-term child and birth was normal. She has had no acute infections and although she lived two years in the Philippines she did not contract malaria. Her father was in the habit of giving her as many as six drinks of whisky a day, and the mother thinks that the "spells" which she has had have followed the abuse of alcohol.

Two years ago she began to have attacks which were diagnosed as petit mal. She usually had from one to fifty of them and has had as high as one hundred a day. The attacks were first noticed at the table. She would stop eating and stare off into space. During the attacks she does not answer when spoken to. The first attacks lasted only a few seconds each, but at the present time they are sometimes much longer. She was examined by two very competent men, who said it was epilepsy. They gave her bromids and advised country life and all the milk and eggs she could take. She was taken to the country and given the medicine prescribed, without improvement. While in the country she would sink to the ground when the attacks came on and at times had as many as one hundred "spells" a day.

The physical examination showed a fairly well-nourished, gracile child of dark complexion. She made quick movements which were not of choreiform character. The general physical examination showed nothing of importance.

The electrical reactions, which were markedly spasmophilic, are shown in Chart 46 (August 3), and Chart 47 (September 12).

On August 3, during the examination in the office, she looked off into space and the pupils became somewhat dilated and the expression blank. The attack lasted about ten seconds, after which she immediately became the active, alert, apparently normal child she was before. She was sitting on the edge of a table from which she did not fall and seemed to have no difficulty in keeping her position. She said nothing during the attack, although she had been talking on and off before. During the attack she seemed to notice that her dress was unbuttoned in the back, although the expression was still vacant. There was no Chvostek phenomenon. The patellar reflexes were very marked. The Achilles tendon reflexes were present and marked.

She was put on a carbohydrate diet without milk or meat and given phosphorus in cod-liver oil, but no sedatives.

The decrease in the number of attacks can be readily seen from the curve extending from Aug. 4 to Sept. 25, 1912. (Chart 48.) On September 12 she

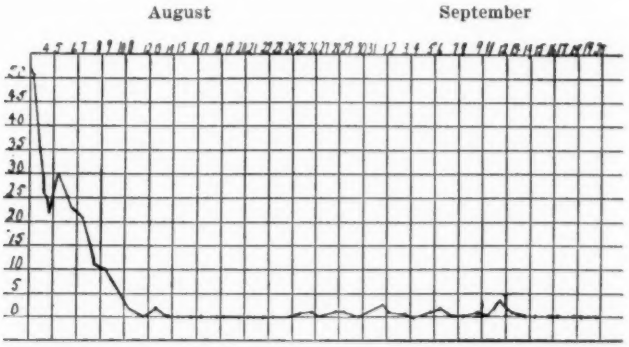


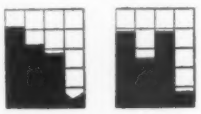

Chart 48.—Decrease in epileptic attacks. Case 14, Aug. 4 to Sept. 25, 1912.

left Minneapolis, but continued with the milk-and-meat free diet, and the mother reported from St. Joseph, Missouri, on Oct. 26, 1912, that she was having about one attack a week and that very slight. The treatment was continued. On Nov. 26, 1912, she reported from Cheyenne, Wyoming, that the child had had no attacks since October 26. The treatment was ordered continued. On Dec. 20, 1912, she reported from Tacoma, Washington, that the child had not had any more attacks and was doing well. During the spring of 1913 she had a recurrence, but she was in the West and there was no opportunity to take her reactions. As the spasmophilic season of the year passed over she improved.

Case 15.—Another case, but with some motor symptoms, which is still under observation with slight improvement, is that of Edith N., aged 11. The mother's brother is said to have had epilepsy at the age of 4 or 5 years, but as he recovered and is now well he may have had spasmophilia. This child began to have attacks two years ago. She was sitting on a table during examination. Without any warning the eyelide dropped, the eyeballs showed nystagmus and turned upward slightly. As she leaned forward there seemed to be an attempt to right herself as one who falls asleep in a chair. The attack lasted from three to five seconds. She seemed normal immediately afterward, but could give no proper description of the attack. She has from twenty to thirty-five of these daily. The electrical reactions may be seen in Chart 49 (January 10). If this case is epilepsy, there is spasmophilia present also, as shown by the electrical reactions.

It is possible that the following case, which shows both petit mal-like attacks and convulsions, may be a link between "repeated absences" and the spasmophilic convulsions. In my opinion, such electric reactions and the Chvostek sign warrant a better prognosis than in epilepsy proper.

CASE 16.—Joe D. was a well-nourished boy of 9 years when first seen in September, 1912. His testicles have not descended. His infant brother was seen by me in typical spasmophilic convulsions and now shows marked anodal hyperirritability. One year before the first examination Joe D. had two or three attacks a day for one week. In these attacks he fell and was rigid and unconscious. The attacks then ceased until five days before this examination. He has had from two to six attacks daily since. His mother says that they manifest themselves at this time as a blank expression which comes over his face for a few seconds. He answers questions at this time but has no recollection of them afterward. During the physical examination he had just such a manifestation as his mother described. He appeared perfectly normal immediately afterward. His electric reactions are shown in Chart 50 (September 12).



49 50

Chart 49.—Edith N., Case 15, Jan. 10, 1913.
Chart 50.—Joe D., Case 16, Sept. 12, 1912.

The Chvostek phenomenon was pronounced. These attacks continued, with some which showed clonic convulsions, until October 10. From that time until the present, June 4, 1913, he has had no more seizures. The history with the electrical reactions and Chvostek phenomenon warrant the diagnosis of spasmophilia.

The diagnosis of spasmophilia rests on the electric reactions, convulsions, tetany, laryngospasm, spasmodic apnea, together with the Trousseau, Chvostek and allied phenomena. Not only have we here an aid in the differentiation of these convulsions from those of major epilepsy, but certain cases of petit mal may belong under this heading.

Although death does occur in the general convulsions and in laryngospasm, under proper treatment the prognosis, so far as life is concerned, is usually favorable. Thiemich and Mann found, however, that about one-third of these cases show later evidences of injury to the mentality.

The accepted treatment consists in the withdrawal of cow's milk with the substitution of breast-milk when possible, or carbohydrates in the shape of gruels, and the administration of cod-liver oil and phosphorus. Sedatives, such as chloral hydrate, may be necessary in the active stages. The calcium therapy is not as yet generally used. The recent studies in this subject will require rewriting of the chapters on convulsions to be found in most of the texts on pediatrics.

Syndicate Building.

# THE VALUE OF THE BLOOD PICTURE IN THE EARLY DIAGNOSIS OF MEASLES, ESPECIALLY IN RELATION TO THE QUESTION OF ISOLATION *

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Measles is one of the most interesting of the specific reaction diseases to study, as it has such a definite incubation period and runs such a definite course, not only in its temperature reaction, but also in the manner of the appearance of the eruption.

Since making some studies with the measles virus, experimentally reproducing it in monkeys, with E. L. Prizer last year, I have been very much interested in carrying out some of our experimental findings with the idea of using these findings for early diagnosis, especially in reference to isolation, and so preventing the spread of ward epidemics in infants' hospitals. I have had two such opportunities in the wards of the Children's Hospital of the Boston Dispensary: one in June, 1912, and a second in February, 1913.

During the first epidemic we had five cases come down with measles and six control cases were followed from the time of first contact. In the second series, there were four cases that came down with measles and four control cases which were open to the same infection and which we were able to study throughout the whole incubation period, but which did not come down with measles; besides in each case we were able to study the blood of the children who brought the infection into the ward. In all of these cases daily white counts were done at the bedside, the time of taking the counts being in the morning; and if there was a marked change in the count from the day before, an afternoon count was usually taken. Smears were taken at these times and counted as soon as the complete counts in the wards were done. In this way we were able to check our results at the end of each day.

In our experimental work of last year, our fourth conclusion was as follows:

> During the pre-eruptive stage of the disease (measles) there is a leukopenia involving the polymorphonuclear neutrophils, the lymphocytes, and the large mononuclear leukocytes. This leukopenia develops in five to ten days after inoculation and may be preceded by a transient lymphocytic and a large mononuclear leukocytosis, which is probably lacking or only poorly developed in the severe form of the reaction, but is strongly developed in less severe cases.

* Submitted for publication Nov. 11, 1913.

These findings are not entirely new (see bibliography), but I was interested to see what their practical application would be in isolating cases before the really infective period of coryza appeared.

As is well known, measles is probably the most infectious disease that is at all prevalent to-day. In fact, next to small-pox, it is probably the most contagious disease that we know anything about. If we hope in any way to prevent the spread of measles, it must be done through an earlier recognition of the disease than is at present possible by clinical methods alone. That is, we must learn to recognize the disease before the stage of lacrimation, coughing and sneezing, and profuse serous nasal discharge, for it is in this early pre-eruptive stage that the infection is most easily carried. In fact, experimentally it has been proven that the blood at this period is more infectious than in the eruptive stage. This study was carried out entirely on infants who were in the hospital mainly as special feeding problems; as such, they were cases of the type which is supposed to contract measles if exposed, and to suffer the worst after-effects. My observations in these nine cases that came down with measles and in the ten cases that were in the wards at the time, but who did not come down with measles, brought me to the following conclusions, which are shown more in detail in the individual protocols and charts:

1. Blood examination under such conditions is of definite value.

2. There is an early change in the blood picture which may be taken as the first evidence of the infection. This consists in a change from the ordinary lymphocytic predominance which exists normally in infants' blood, to a relative increase in the percentage count of the neutrophilic type of cell. Though there is an actual diminution, here also the diminution in the lymphocytes far exceeds that of the neutrophils, so that there is a complete reversal of the blood picture. The normal percentage of lymphocytes in infants' blood ranges from about 55 to 70 per cent. of the white blood-cells; whereas the neutrophils range from about 25 to 30 per cent., the large mononuclear cells ranging from about 8 to 15. The earliest sign which appears in the blood of an infant coming down with measles is a beginning reversal of this picture. The reversal usually begins about a week before any visible symptoms of infection occur. The actual reversal has occurred at least forty-eight hours before the earliest signs are visible, that is, Koplik spots, coryza or coughing. There is also a definite constant leukopenia present which sometimes appears eight days before any physical signs, and sometimes appears simultaneously with the physical signs. For this reason it is not so reliable a diagnostic method as the cell picture, which is far more constant and reliable as a determining factor in making an early diagnosis.

3. There appears an ever increasing number of disintegrated cells, which first make their appearance about the time the cell picture begins

to change. These disintegrated cells may not be specific, and probably are not specific in measles; but with the reversal of the blood picture, they are to be counted as a definite factor in the early diagnosis. They appear to be in many instances large, swollen cells, with protoplasm breaking up and the nucleus, as it were, water-logged or breaking up into fragments. The shape varies from round to oval, with no sharply defined outline. Granulations are abundant, and they can be seen separating from the nuclei.

I feel sure that this combination finding in blood in suspected cases will be of considerable value in the early detection, therefore in the early isolation, of suspected cases; and that this method has been able in my hands to cut down the probable incidence of measles in my ward by 25 or 50 per cent., as it is not an unusual thing to have every child exposed to measles come down with it; and every new case adds to the chances of the others in the ward coming down.

In both these epidemics, there were no secondary cases, so that I felt sure that by this close observation, we were able to isolate at such an early period that these nine cases which came down were not sources of secondary infection to the rest of the children in the ward. I was so impressed by this fact during our first epidemic, in June, that in the later epidemic I continued to admit cases to the ward, watching the old cases in this close manner, with the result, as I said, that we had no secondary infection.

## PROTOCOLS

### FIRST SERIES OF CASES

J. D. (Chart 1), aged 10 months, Hospital No. 912. Admitted to the hospital May 20, 1912. Original case of measles occurred in the ward on June 3. J. D. was a case of general septicemia of low grade with a marked bacteriuria. She had been running a constant white count which, on May 21 (the day after admission) was 35,000 white blood-count. On June 3 it was 27,000. As will be seen by her chart, initial temperature occurred on the morning of the 14th, just eleven days after exposure without any drop in her white count. Koplik spots appeared on the 16th, and the rash was profuse on the 19th. At no time did her white count fall below 21,000. This is the only case in which there was no drop in the white count and practically no change in the blood picture, though the blood picture is not normal, as there is an increase of polymorphonuclear cells. This, however, was present before the exposure to measles, and was probably due to the septicemia from which she was suffering. This is the only patient of the nine cases of infection with measles who died, death occurring on the 24th, eleven days after the initial temperature of measles. This could be classed under complicated cases and the blood findings could not be counted as typical in any way.

J. De Y. (Chart 2), 3 years old, Hospital No. 901. Was admitted to the hospital on May 31. First exposure to measles on June 3. On that day he had a white count of 9,000. The next day his white count dropped to 6,400, and he was isolated with beginning reversal of blood picture. Koplik spots appeared on the 6th, the earliest I have seen Koplik appear in any case, and rash appeared on the 7th. Reversal appeared on the 4th and continued very markedly through to the 11th, when, as will be seen, leukopenia also began to disappear. A possible

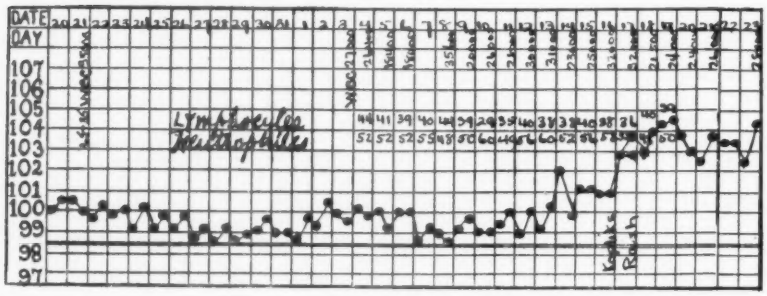

Chart 1.—Temperature curve and blood-count in case of J. D., aged 10 months, No. 912, admitted May 20, 1912. Series 1.

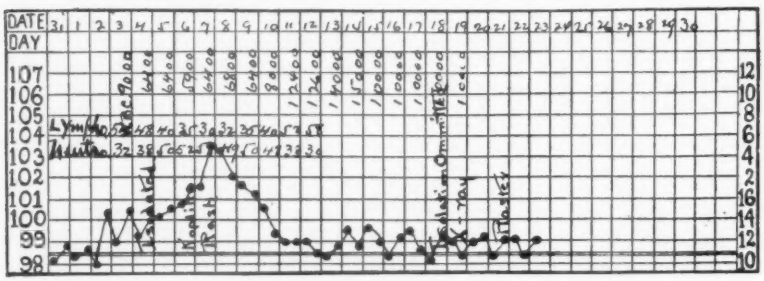

Chart 2.—Temperature curve and blood-count in case of J. DeY., aged 3 years, No. 901, admitted May 31, 1912. Series 1.

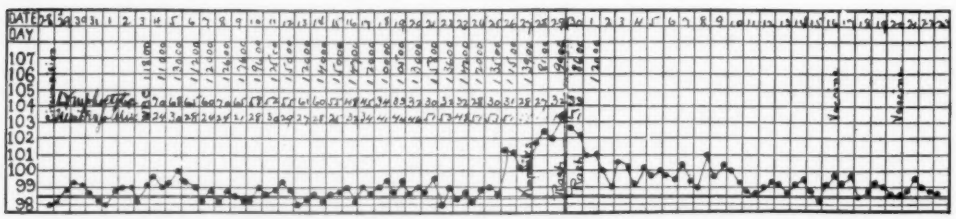

Chart 3.—Temperature curve and blood-count in case of J. N., aged 8 months, No. 925, admitted May 28, 1912. Series 1.

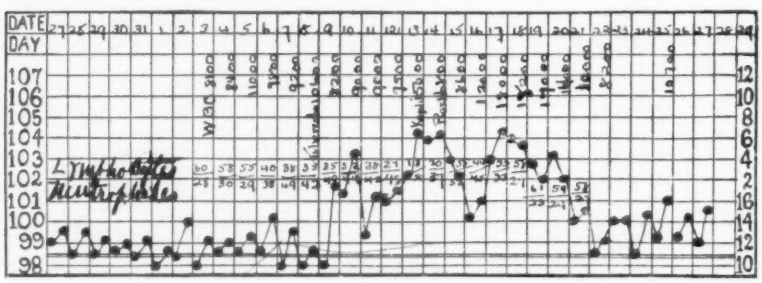

Chart 4.—Temperature curve and blood-count in case of J. C., aged 1½ years, No. 922, admitted May 27, 1912. Series 1.

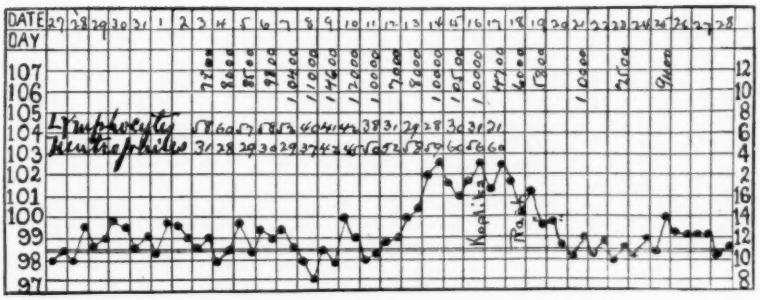

Chart 5.—Temperature curve and blood-count in case of A. R., aged 10 months, No. 841, admitted May 27. Series 1.

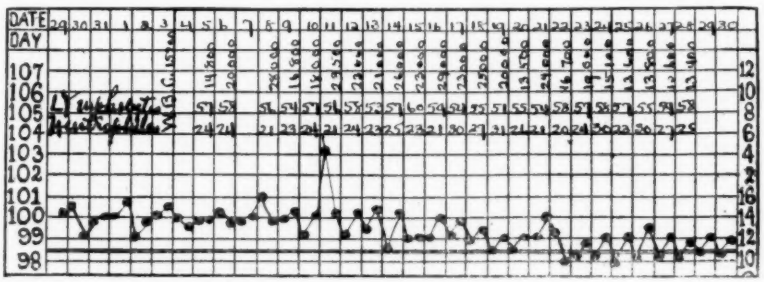

Chart 6.—Temperature curve and blood-count in case of J. S., aged 10 months, No. 927, admitted May 29, 1912. Control case, Series 1.

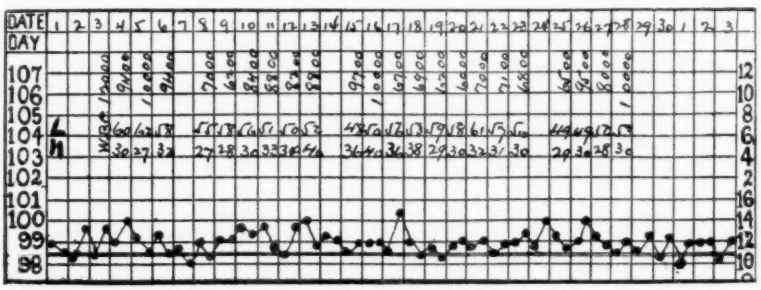

Chart 7.—Temperature curve and blood-count in case of L. D., aged 2½ years, No. 904; admitted May 8, 1912. Control case, Series 1. L = lymphocytes; N = neutrophils.

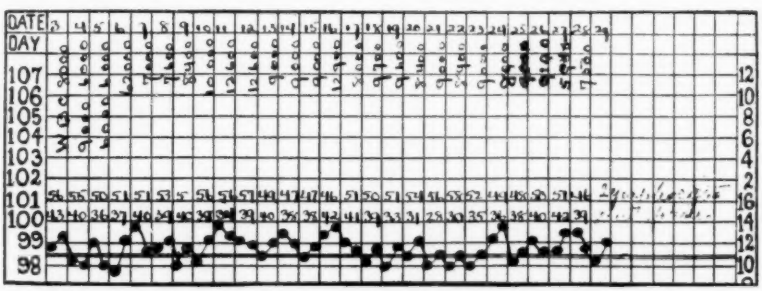

Chart 8.—Temperature curve and blood-count in case of M. H., aged 3 months, No. 885, admitted April 16. Control case, Series 1.

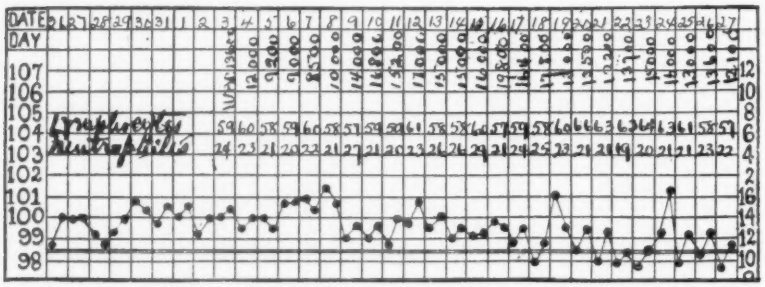

Chart 9.—Temperature curve and blood-count in case of N. W. M., aged 14 years, No. 921, admitted May 26, 1912. Control case, Series 1.

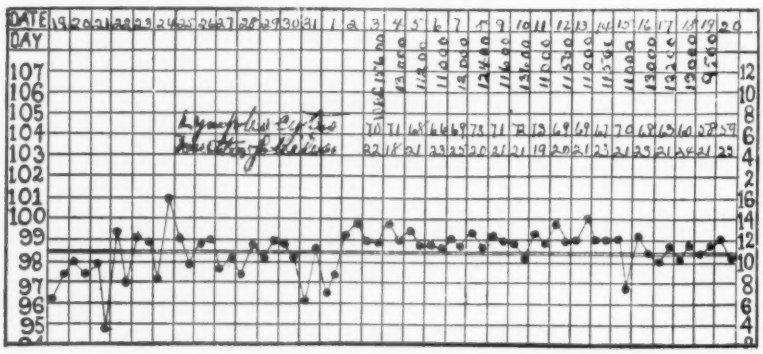

Chart 10.—Temperature curve and blood-count in case of E. T., aged 3 months, No. 910, admitted May 19, 1912. Control case, Series 1.

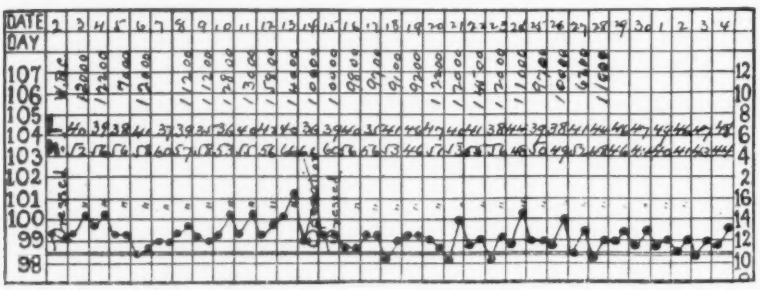

Chart 11.—Temperature curve and blood-count in case of M. S., aged 12 months, No. 899, admitted April 30, 1912. L = lymphocytes; N = neutrophils. Series 1.

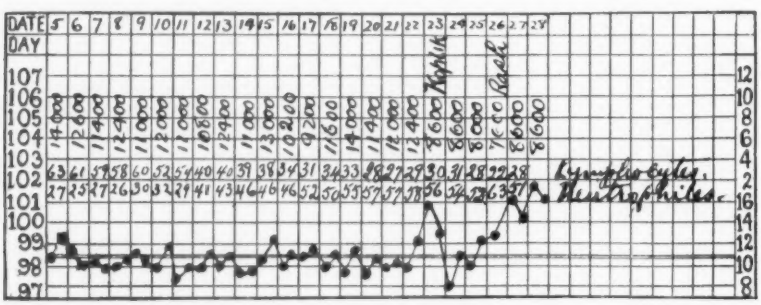

Chart 12.—Temperature curve and blood-count in case of Helen McL., aged 6 months, No. 1146, admitted January 25. Series 2.

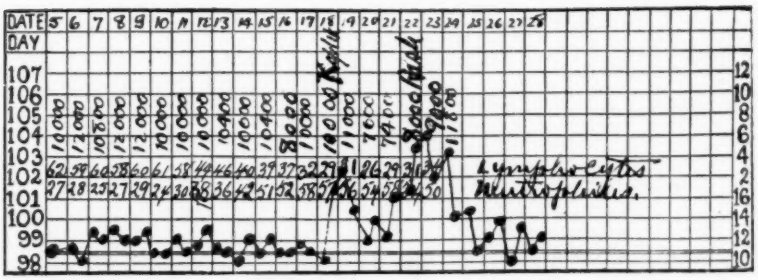

Chart 13.—Temperature curve and blood-count in case of Alice M., aged 9 months, No. 1044, admitted Oct. 8, 1912. Series 2.

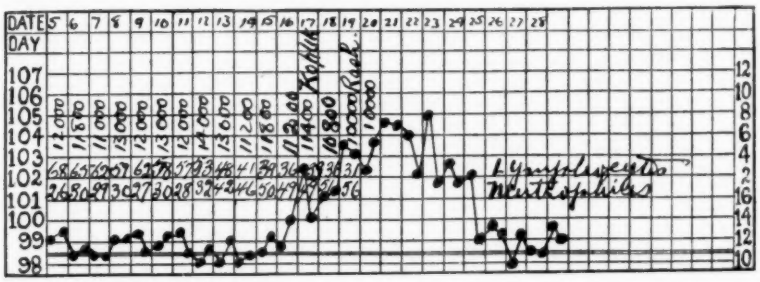

Chart 14.—Temperature curve and blood-count in case of Mary M., aged 11 months, No. 1075, admitted Nov. 9, 1912. Series 2.

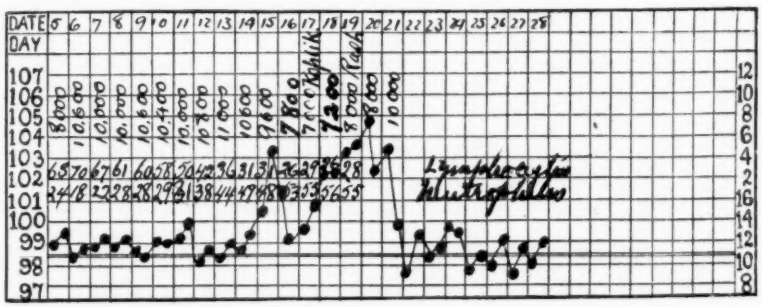

Chart 15.—Temperature curve and blood-count in case of Paul S., aged 17 months, No. 1110, admitted Dec. 14, 1912. Series 2.

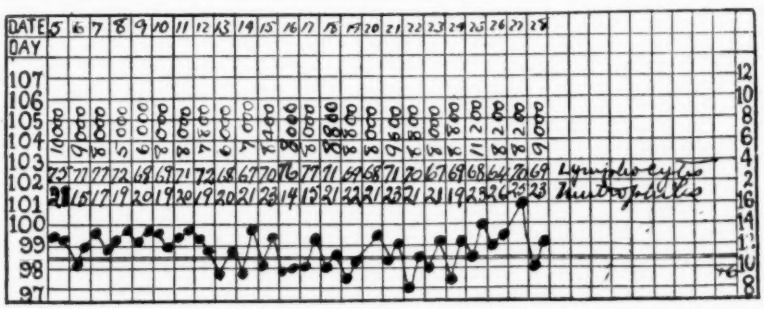

Chart 16.—Temperature curve and blood-count in case of Edward S., aged 16 months, No. 1125, admitted Jan. 6, 1913. Control case, Series 2.

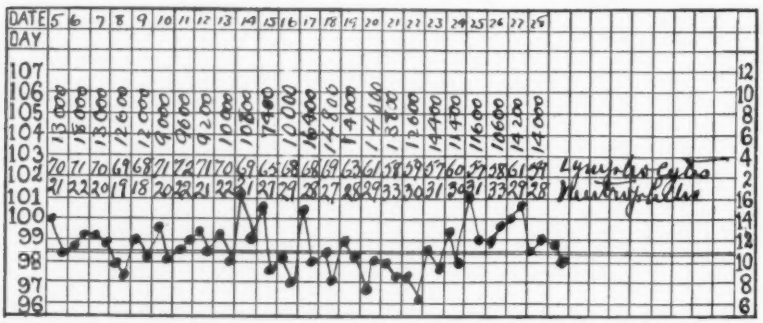

Chart 17.—Temperature curve and blood-count in case of James M., aged 3 months, No. 1112, admitted Dec. 18, 1912. Control case, Series 2.

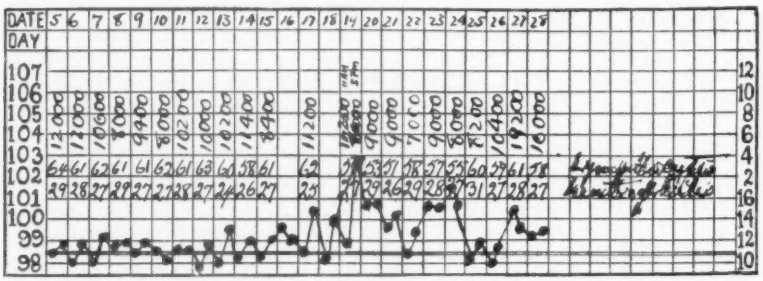

Chart 18.—Temperature curve and blood-count in case of Hyman S., aged 11 months, No. 1140, admitted January 18. Control case. Series 2.

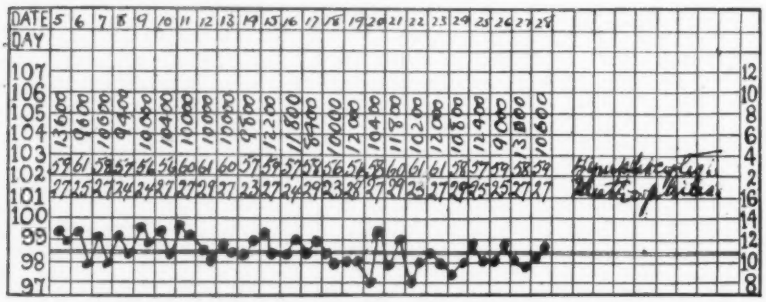

Chart 19.—Temperature curve and blood-count in case of Joseph N., aged 4 months, No. 1145, admitted January 23. Series 2.

explanation of course is that he entered during the incubation period; if so, our blood examinations certainly prevented infecting the ward.

J. N. (Chart 3), 8 months old, Hospital No. 925. Was admitted to the hospital on May 28, 1912. First exposure to the measles was on June 3. This was a poorly nourished child, weighing 9 pounds and 3 ounces on admission. His white blood-count on the 3d was 11,800. He first showed temperature rise on the morning of the 26th; Koplik spots on the morning of the 27th, and rash on the morning of the 28th. He had his first drop in white count on the 18th and 19th, with reversal of the blood picture. This was followed by a rise in the total number of white cells, but the reversal continued to increase. Why he had such

a persistently high white count throughout the pre-eruptive stage, except for these two days, it is hard to say, unless it is that his infection was so markedly delayed, the first appearance being twenty-three days after infection.

J. C. (Chart 4), 1½ years old, Hospital No. 922. Admitted to the hospital May 27. First exposure to measles was on June 3. White count on that day was 8,100. He had a persistently low white count from the start; the reversal started on the 6th and continued through to the time of the appearance of the eruption on the 14th. This case was put into isolation on the 9th on account of his persistently low white count and ele ation of temperature that evening, though Koplik spots did not appear until four days after this.

A. R. (Chart 5), 10 months old, Hospital No. 841. Admitted to the hospital on May 27th; first exposed to measles on June 3. On that day his white count was 7,800. This remained low for four days, when it went approximately back to normal. On the 11th the reversal started; on the 12th there was a marked leukopenia; the reversal continued throughout the whole period of the eruption, which was a remarkably severe one.

During this epidemic there were six other cases in the ward which were open to the first infection on June 3. Two of these patients showed absolutely no change from the normal, either in the total white count or in the blood picture throughout this period. The chart illustrating this is that of J. S. (Chart 6), on which it is seen that, though there was a rise in temperature on the 11th which might have been indicative of beginning infection, there was no fall in the white count, and there was no reversal of the blood picture.

However, there were four cases in this series which did show drops at various times. The most marked of these is that of L. D. (Chart 7), 2½ years old, Hospital No. 904, a case supposedly of general pulmonary tuberculosis. In this case, as will be seen, there is an irregular drop in the white count; but instead of there being a reversal of the blood picture, the lymphocytes were increased throughout.

Of the other control cases of this series, M. H. (Chart 8), aged 3 months, Hospital No. 885, first exposure June 3, showed a drop in white count on several occasions to as low as 6,000, but there was no reversal in the blood picture. During this first epidemic I had this child isolated each time there was a drop as low as 7,000; but she showed at no time any signs of measles, either in typical temperature, coryza, cough, Koplik spots or eruption.

N. W. M. (Chart 9), 1 year old, Hospital No. 921. This was a feeding case. Date of first exposure, June 3. On June 6 he showed a drop from an average of 13,000 to 9,000. On this account he was isolated, though he showed no signs of measles at any time. He never developed any eruption, never had any coryza, cough or lacrimation, and had no reversal in blood picture.

E. T. (Chart 10), aged 3 months, Hospital No. 910. First exposure was on June 3. She showed no fall in white count, no signs of measles, coryza, lacrimation, Koplik spots or eruption. No reversal in blood picture.

M. S. (Chart 11), control case, first series, aged 12 months, Hospital No. 899. Date of first exposure, June 3. This child was suffering from a low grade osteomyelitis of the shoulder. She had two drops to 7,000 on the 5th and 27th, respectively, but there was at no time any reversal in the blood picture.

## SECOND SERIES OF CASES

The second series had their first exposure to infection on Feb. 5, 1913.

H. McL. (Chart 12), aged 6 months, Hospital No. 1146. She showed her first drop on the 17th, with reversal of blood picture beginning on the 12th, quite marked by the 14th. Greatest leukopenia occurred with the height of the rash on the 26th, Koplik spots having appeared on the 23d. The reversal continued throughout the entire period of the infection.

A. M. (Chart 13), aged 9 months, Hospital No. 1044. First exposure on February 5. She showed her first reversal on the 12th. This was very marked by the 16th, when there was also the first drop in the white count. Koplik spots appeared on the 18th; the rash was profuse by the 22d, the lowest white blood counts coming on the 20th and 21st, with a reversal in the blood picture continuing throughout the infection.

M. M. (Chart 14), aged 11 months, Hospital No. 1075. First exposure on the 5th. First showed reversal on the 14th; also had at the same time a drop in the white count, though the drop was at no time very marked. The reversal was quite pronounced on the 15th, when she was isolated; Koplik spots did not appear until the 17th, and the rash on the 19th.

P. S. (Chart 15), 17 months old, Hospital No. 1110. First exposure to infection on the 5th, on which day there was a white count of 8,000. The next day the white count was 9,600, around which it continued until there was a marked drop on the 16th. First rise in temperature occurred on the 15th. The reversal in the blood picture appeared on the 11th. The following day isolation was instituted. In this case there were no Koplik spots, no coryza and no rash until the 17th, on which day a few Koplik spots appeared. Koplik spots, coryza and photophobia being marked on the 18th, and the rash on the 19th.

In this second series there were four control cases followed throughout this period of observation.

E. S. (Chart 16), 16 months old, Hospital No. 1125. First exposure on the 5th. In this case it will be seen that there were a number of drops in the white count, but at no time was there any reversal in the blood picture. In fact there was an increase in the percentage of lymphocytes throughout. The case was one of supposed general tuberculosis. He gave a strongly positive tuberculin reaction.

J. M. (Chart 17), aged 3 months, Hospital No. 1112. First exposure on the 5th. There was a drop in the white count on the 10th, which continued until there was a marked drop on the 15th, with temperature rise on the 14th. There was, however, no reversal in the blood picture. He was, however, kept isolated throughout this period. There were no signs of measles; no coryza, lacrimation or Koplik spots. No eruption occurred at any time and he was allowed out of isolation on the 17th.

H. S. (Chart 18), 11 months old, Hospital No. 1140. First exposure on the 5th. Had drop in white count on the 15th without any reversal in blood picture. Temperature began to rise on the 17th. On the 19th there was also another drop in the afternoon, the white count being taken on account of marked rise of afternoon temperature, and a very marked leukopenia on the 22d. This low white count continued until the 25th, with temperature rise. Throughout this period, however, his appearance was not at all suspicious of measles; he had no coryza, lacrimation, Koplik's spots nor eruption. There was no reversal of the normal blood picture. This case represents a control case.

Joseph N. (Chart 19), 4 months old, Hospital No. 1145. First exposure on the 5th. Had several drops in white count, but no reversal in blood picture. On the 17th had quite a marked leukopenia, 8,400; no temperature reaction; no coryza, photophobia, lacrimation, or Koplik's appeared on this day or at any time following. Control case.

University Hospital.

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